Chemoselective Activation of sp^3 vs sp^2 C–H Bonds with Pd(II)

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Supporting Information

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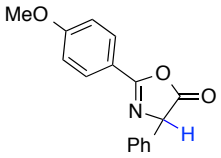
General Considerations

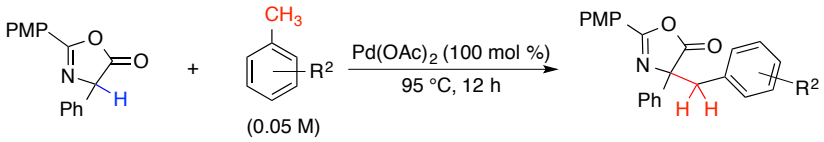
All non-aqueous reactions were carried out under an atmosphere of dry argon unless otherwise noted. Commercial reagents were used as received without additional purification unless otherwise noted. Dichloromethane was distilled from CaH_2, and toluene was distilled from metallic sodium prior to use. Anhydrous 1,4-dioxane was purchased from Sigma Aldrich as 100 mL sure-seal bottles and stored in the glovebox. Activated carbon (Darco G-60) was dried overnight at 80 °C *in vacuo*. Reactions were monitored by thin layer chromatography (TLC) using Silicycle glass-backed TLC plates with 250 μm silica and F254 indicator. Visualization was accomplished by UV light.

^{1}H NMR and ^{13}C NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.26 ($CDCl_3$) for ^{1}H and δ 77.16 ($CDCl_3$) for ^{13}C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad singlet, m = multiplet), coupling constants, and number of protons. High resolution mass spectra were obtained using a VG autospec with an ionization mode of either ESI or CI. Infrared spectra are reported in cm^{-1}. Melting points are uncorrected. Unless otherwise noted, yields refer to isolated material on the basis of product purity (≥95%) by ^{1}H NMR following silica gel chromatography with Silica-P flash silica gel (50-63 μm mesh particle size).



2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (1). *N*-*para*-methoxyphenyl-phenylglycine (500 mg, 1.8 mmol) was added to a flame dried 25 mL round bottom flask equipped with a stirbar under an argon atmosphere. The mixture was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCl) (441 mg, 2.3 mmol) was added and the mixture was allowed to warm to ambient temperature. After 1 h at ambient temperature, the mixture was diluted with CH_2Cl_2 (30 mL), washed with H_2O (2 x 30 mL), 0.1 M NaOAc (2 x 30 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* providing **1** (443 mg) in 94% yield as a light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 8.9 Hz, 2H), 7.47-7.33 (m, 5H), 7.01 (d, J = 8.9 Hz, 2H), 5.49 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 163.6, 162.4, 133.9, 130.2, 129.1, 128.8, 127.0, 118.1, 114.4, 68.3, 55.7; IR (film) 3008, 2935, 2839, 1827, 1648, 1608, 1512, 1260 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{13}NO_3$ $[M]^+$ m/z = 267.0895; found 267.0895.

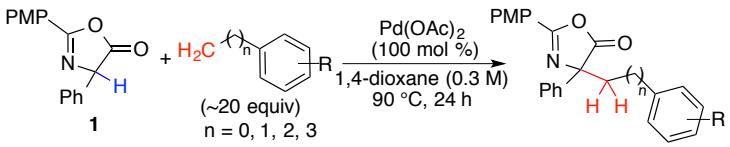
General procedure A – benzylation with stoichiometric Pd in neat tolyl analog



Phenylglycine azlactone **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. The indicated tolyl analog (0.05 M, ~10.5 mmol) was added to

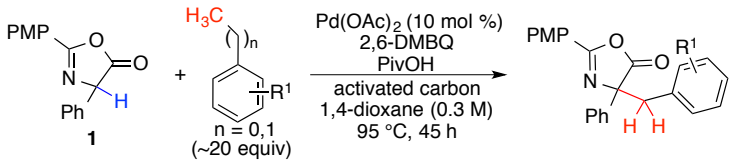
the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox, placed in a 95 °C oil bath. After 6 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography to afford the alkylated azlactone.

General procedure B – alkylation with stoichiometric Pd in 1,4-dioxane



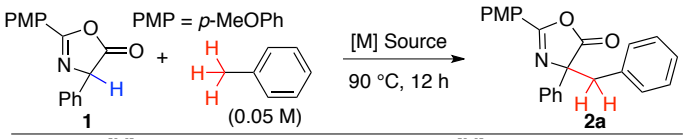
Phenylglycine azlactone **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. The indicated tolyl analog (1.12 mmol) and 1,4-dioxane (200 μL, 0.3 M) were added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 90 °C oil bath. After 24 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography to afford the alkylated azlactone.

General procedure C – alkylation with catalytic Pd in 1,4-dioxane



Phenylglycine azlactone **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol), PivOH (5.7 mg, 0.056 mmol), 2,6-DMBQ (7.6 mg, 0.056 mmol) and activated carbon (13 mg, 10x weight of Pd) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. The indicated tolyl analog (1.12 mmol) was added to the mixture followed by 1,4-dioxane (467 μL, 0.12 M). The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 45 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), and purified directly by column chromatography to afford the alkylated azlactone.

Metal sources for C–H activation of toluene (Table 1)



entry	[M] source (100 mol %)	yield (%)[a]	entry	[M] source (100 mol %)	yield (%)[a]
1	$Au(OAc)_3$[b]	0	7	$Pd(TFA)_2$	81
2	$Cu(OAc)_2$[b]	0	8	$PdCl_2$	0
3	$Rh_2(OAc)_4$[b]	0	9	$PdCl_2(MeCN)_2$	0
4	Ni(OAc)2[b]	0	10	$PdCl_2(COD)_2$	0
5	$[Pt_4(OAc)_8]$•HOAc[b]	0	11	$[Pd(allyl)Cl_2]_2$	0
6	$Pd(OAc)_2$	77	12	Pd_2dba_3	0

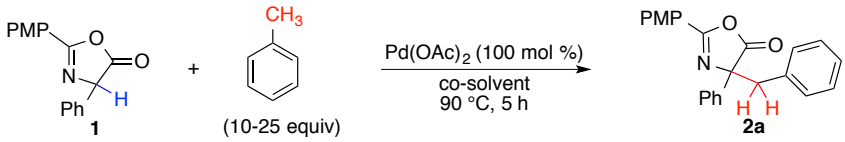
[a]Isolated yield. [b]Azlactone dimer as substrate, 20 mol % metal source, 5 h.

For Table 1, entries 1-5: Phenylglycine azlactone dimer **8** (10 mg, 0.019 mmol) was added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. The indicated metal source[1] (0.008 mmol) was added followed by toluene (377 μL). The microwave vial was sealed with a Teflon cap, removed from the glovebox, placed in a 90 °C oil bath. After 5 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in

hexanes, and concentrated *in vacuo*. The resulting residues were analyzed by ^{1}H NMR spectroscopy and each experiment provided only unreacted phenylglycine azlactone dimer **8**.

For Table 1, entries 6-12: General procedure A was followed with phenylglycine azlactone **1** (10 mg, 0.038 mmol), the indicated metal source (0.038 mmol) and toluene (750 μL). After 12 h at 90 °C oil bath, the resulting residues were analyzed by ^{1}H NMR spectroscopy: entries 6 and 7 provided full conversion to benzylated product **2a**, entry 8 provided full conversion to phenylglycine azlactone dimer **8** and entries 9-11 provided minimal phenylglycine azlactone dimer **2a** and decomposition of phenylglycine azlactone **1**.

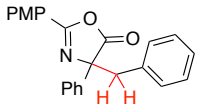
Table S1. Screen of co-solvents.



General procedure B was followed using **1** (10 mg, 0.037 mmol) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in toluene (0.37 or 0.93 mmol) and co-solvent (133 μL) at 90 °C for 5 h.

entry	co-solvent (0.3 M)	toluene (equiv)	conv (%)[a]	entry	co-solvent (0.3 M)	toluene (equiv)	conv (%)[a]
1	none	25	>90	5	none	10	~90 (68)[b]
2	benzene	25	>90	6	benzene	10	~90 (65)[b]
3	cyclohexane	25	>90	7	1,4-dixoane	10	25[c]
4	1,4-dioxane	25	>90				

[a]Determined by ^{1}H NMR. [b]Isolated yield. [c]3:1 mixutre of phenylglycine azlactone and desired product.

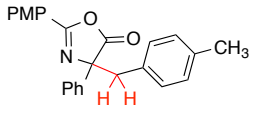


4-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (2a). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in toluene (118 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **2a** (16.5 mg) in 83% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.24-7.12 (m, 5H), 6.93 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.51 (d, J = 13.4 Hz, 1H), 3.44 (d, J = 13.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.4, 134.4, 130.6, 129.9, 128.8, 128.4, 128.2, 127.4, 126.0, 118.2, 114.2, 75.6, 55.6, 47.4; IR (film) 3031, 2925, 1813, 1653, 1608, 1513, 1260 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{12}NO_3$ $[M\text{-}C_7H_7]^+$ m/z = 266.0817; found 266.0826.

4-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (2a). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in toluene (474 μL, 4.5 mmol). The mixture was allowed to stir at 90 °C for 5 h and purification by column chromatography provided **2a** (16.5 mg) in 83% yield. See above for characterization.

4-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (2a). General procedure C was followed using **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol), PivOH (5.7 mg, 0.056 mmol), 2,6-DMBQ (7.6 mg, 0.056 mmol) and activated carbon (13 mg, 10x weight of Pd) in toluene (118 μL, 1.12 mmol) and 1,4-dioxane (467 μL, 0.12 M) at

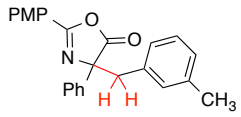
95 °C for 45 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2a** (16.3 mg) in 82% yield. See above for characterization.



2-(4-Methoxyphenyl)-4-(4-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2b). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **2b** (16.2 mg) in 78% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d J = 8.8 Hz, 2H), 7.78 (d, J = 7.9 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 7.9 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.47 (d, J = 13.6 Hz, 1H), 3.40 (d, J = 13.4 Hz), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.6, 136.9, 131.3, 130.4, 130.0, 128.9, 128.8, 128.3, 126.0, 118.3, 114.2, 75.7, 55.6, 47.1, 21.2; IR (film) 3007, 2962, 2927, 1813, 1654, 1608, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ m/z = 372.1600; found 372.1594.

2-(4-Methoxyphenyl)-4-(4-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2b). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-xylene (546 μL, 4.5 mmol). The mixture was allowed to stir at 90 °C for 12 h and purification by column chromatography provided **2b** (17.2 mg) in 83% yield. See above for characterization.

2-(4-Methoxyphenyl)-4-(4-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2b). General procedure C was followed using **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol), PivOH (4.6 mg, 0.045 mmol), 2,6-DMBQ (6.1 mg, 0.045 mmol) and 3 Å MS (12 mg, 3x weight of Pd) in *para*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (187 μL, 0.3 M) at 95 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2b** (8.1 mg) in 39% yield. See above for characterization.

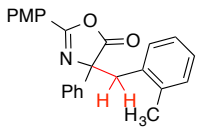


2-(4-Methoxyphenyl)-4-(3-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2c). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *meta*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **2c** (16.3 mg) in 78% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d J = 8.9 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.08-7.00 (m, 3H), 6.96-6.92 (m, 3H), 3.85 (s, 3H), 3.47 (d, J = 13.2 Hz, 1H), 3.40 (d, J = 13.2 Hz), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.5, 137.6, 134.3, 131.5, 129.9, 128.8, 128.4, 128.1, 128.0, 127.5, 126.0, 118.3, 114.2, 75.6, 55.6, 47.5, 21.4; IR (film) 3062, 2929, 1813, 1653, 1604, 1512, 1257 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ m/z = 372.1600; found 372.1600.

2-(4-Methoxyphenyl)-4-(3-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2c). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *meta*-xylene (546 μL, 4.5 mmol). The mixture was allowed to stir at 90 °C for

12 h and purification by column chromatography provided **2c** (15.6 mg) in 75% yield. See above for characterization.

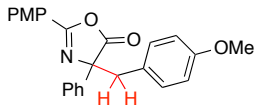
2-(4-Methoxyphenyl)-4-(3-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2c). General procedure C was followed using **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol), PivOH (4.6 mg, 0.045 mmol), 2,6-DMBQ (6.1 mg, 0.045 mmol) and 3 Å MS (12 mg, 3x weight of Pd) in *meta*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (187 μL, 0.3 M) at 95 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2c** (11.2 mg) in 54% yield. See above for characterization.



2-(4-Methoxyphenyl)-4-(2-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2d). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *ortho*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **2d** (8.4 mg) in 40% yield as a yellow oil. See below for characterization.

2-(4-Methoxyphenyl)-4-(2-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (2d). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *ortho*-xylene (546 μL, 4.5 mmol). The mixture was allowed to stir at 90 °C for 12 h and purification by column chromatography provided **2d** (14 mg) in 67% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d J = 8.8 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 7.04-6.99 (m, 3H), 6.92 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 3.55 (d, J = 13.7 Hz, 1H), 3.51 (d, J = 13.7 Hz, 1H), 2.39

(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 163.2, 159.4, 138.8, 138.1, 133.1, 130.8, 130.5, 129.9, 128.8, 128.3, 127.5, 126.0, 125.7, 118.3, 114.3, 76.2, 55.6, 44.1, 20.2; IR (film) 2963, 2928, 1813, 1653, 1609, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ *m/z* = 372.1600; found 372.1588.

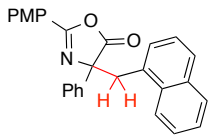


2-(4-Methoxyphenyl)-4-(4-methoxybenzyl)-4-phenyloxazol-5(4*H*)-one (2e). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-methylanisole (141 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **2e** (15.4 mg) in 71% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.45 (d, *J* = 13.6 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 163.3, 159.7, 158.9, 138.5, 131.7, 129.9, 128.8, 128.3, 126.5, 126.0, 118.3, 114.3, 113.6, 75.8, 55.6, 55.3, 46.7; IR (film) 2961, 2926, 2851, 1812, 1760, 1655, 1610, 1513, 1259 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}NO_4$ $[M+H]^+$ *m/z* = 388.1549; found 388.1551.

2-(4-Methoxyphenyl)-4-(4-methoxybenzyl)-4-phenyloxazol-5(4*H*)-one (2e). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-methylanisole (566 μL, 4.5 mmol). The mixture was allowed to stir at 90

°C for 5 h and purification by column chromatography provided **2e** (14 mg) in 67% yield. See above for characterization.

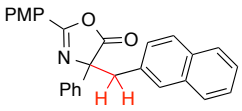
2-(4-Methoxyphenyl)-4-(4-methoxybenzyl)-4-phenyloxazol-5(4*H*)-one (2e). General procedure C was followed using **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol), PivOH (4.6 mg, 0.045 mmol), 2,6-DMBQ (6.1 mg, 0.045 mmol) and 3 Å MS (12 mg, 3x weight of Pd) in *para*-methylanisole (141 μL, 1.12 mmol) and 2-methyl-2-butanol (187 μL, 0.3 M) at 95 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2e** (9.1 mg) in 42% yield. See above for characterization.



2-(4-Methoxyphenyl)-4-(naphthalen-1-ylmethyl)-4-phenyloxazol-5(4*H*)-one (2f) General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 1-methylnaphthalene (159 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **2f** (15.5 mg) in 68% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.46-7.34 (m, 5H), 7.30 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.9 Hz, 2H), 4.02 (d, J = 13.7 Hz, 1H), 3.94 (d, J = 13.7 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 163.0, 159.4, 138.7, 133.8, 132.9, 131.0, 129.8, 129.0, 128.9, 128.4, 128.4, 128.4, 126.0, 125.6, 125.5, 125.4, 125.2, 118.0,

114.0, 76.2, 55.5, 43.6; IR (film) 2926, 2051, 1812, 1652, 1609, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$ *m/z* = 408.1600; found 408.1612.

2-(4-Methoxyphenyl)-4-(naphthalen-1-ylmethyl)-4-phenyloxazol-5(4*H*)-one (2f). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 1-methylnaphthalene (638 μL, 4.5 mmol). The mixture was allowed to stir at 90 °C for 12 h and purification by column chromatography provided **2f** (14.8 mg) in 65% yield. See above for characterization.



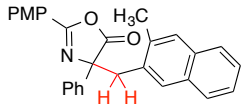
2-(4-Methoxyphenyl)-4-(naphthalen-2-ylmethyl)-4-phenyloxazol-5(4*H*)-one (2g) General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2-methylnaphthalene (160 mg, 1.12 mmol) and 1,4-dioxane (200 μL) at 95 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2g** (22 mg) in 96% yield as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.80 (m, 4H), 7.74-7.70 (m, 2H), 7.68 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.45-7.37 (m, 4H) 7.35 (t, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 3.68 (d, *J* = 13.5 Hz, 1H) 3.61 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.3, 159.9, 138.6, 133.3, 132.7, 132.2, 130.0, 129.6, 128.8, 128.7, 128.4, 128.0, 127.6, 127.6 126.0, 126.0, 125.8, 118.2, 114.2, 75.7, 55.6, 47.5; IR (film) 3057, 2927, 1813, 1654, 1609, 1511, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$ *m/z* = 408.1600; found 408.1590.

2-(4-Methoxyphenyl)-4-(naphthalen-2-ylmethyl)-4-phenyloxazol-5(4*H*)-one (2g). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg,

0.056 mmol) in 2-methylnaphthalene (643 mg, 4.5 mmol). The mixture was allowed to stir at 90 °C for 12 h and purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2g** (17.8 mg) in 78% yield. See above for characterization.

2-(4-Methoxyphenyl)-4-(naphthalen-2-ylmethyl)-4-phenyloxazol-5(4*H*)-one (2g)

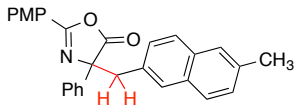
General procedure C was followed using **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol), PivOH (5.7 mg, 0.056 mmol), 2,6-DMBQ (7.6 mg, 0.056 mmol), activated carbon (13 mg, 10x weight of Pd) and 2-methylnaphthalene (159 mg, 1.12 mmol) and 1,4-dioxane (467 μL, 0.12 M) at 95 °C for 45 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2g** (20.1 mg) in 88% yield. See above for characterization.



2-(4-Methoxyphenyl)-4-((3-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (2h). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2,3-dimethylnaphthalene (175 mg, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided unreacted 2,3-dimethylnapthalene (~150 mg) and **2h** (23.4 mg) in 98% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.4 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.68-7.61 (m, 3H), 7.51 (s, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.39-7.30 (m, 3H), 6.87 (d, J = 8.6 Hz, 2H), 3.82 (s, 3H), 3.72 (d, J = 13.7 Hz, 1H), 3.67 (d, J = 13.7 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 163.2, 159.5, 144.8, 138.9, 136.1, 133.0, 132.2, 132.0, 129.9, 128.9, 128.4, 128.3, 127.7, 126.8, 126.0, 125.9,

125.1, 118.2, 114.2, 76.4, 55.6, 44.0, 20.8; IR (film) 3057, 2961, 2932, 1813, 1653, 1609, 1512, 1259 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{24}NO_3$ $[M+H]^+$ *m/z* = 422.1756; found 422.1758.

2-(4-Methoxyphenyl)-4-((3-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (2h). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2,3-dimethylnaphthalene (706 mg, 4.5 mmol). The mixture was allowed to stir at 90 °C for 12 h and purification by column chromatography provided **2h** (18.9 mg) in 80% yield. See above for characterization.

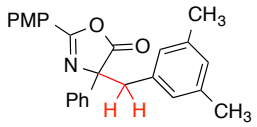


2-(4-Methoxyphenyl)-4-((6-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (2i). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2,6-dimethylnaphthalene (175 mg, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided unreacted 2,6-dimethylnaphthalene (~150 mg) and **2i** (18.1 mg) in 76% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.79 (m, 4H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.48 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.66 (d, *J* = 13.5 Hz, 1H), 3.58 (d, *J* = 13.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 163.2, 159.8, 138.6, 135.5, 132.9, 131.6, 131.2, 130.0, 129.3, 128.8, 128.8, 128.4, 128.2, 127.8, 126.9, 126.6, 126.0, 118.2, 114.2, 75.8, 55.6, 47.5,

21.8; IR (film) 3055, 2923, 2852, 1812, 1653, 1609, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{24}NO_3$ $[M+H]^+$ *m/z* = 422.1756; found 422.1751.

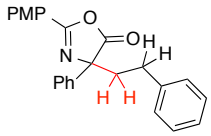
2-(4-Methoxyphenyl)-4-((6-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (2i). General procedure A was followed with **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2,6-dimethylnaphthalene (706 mg, 4.5 mmol). The mixture was allowed to stir at 90 °C for 12 h and purification by column chromatography provided **2i** (18.9 mg) in 80% yield. See above for characterization.

2-(4-Methoxyphenyl)-4-((6-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (2i). General procedure C was followed using **1** (12 mg, 0.044 mmol), $Pd(OAc)_2$ (1.0 mg, 0.0044 mmol), PivOH (4.5 mg, 0.044 mmol), 2,6-DMBQ (5.9 mg, 0.044 mmol), and 2,6-dimethylnaphthalene (345 mg, 2.2 mmol) at 110 °C for 15 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **2i** (8.3 mg) in 45% yield. See above for characterization.



4-(3,5-dimethylbenzyl)-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (2j). General procedure A was followed using **1** (10 mg, 0.037 mmol) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in mesitylene (750 μL, 5.4 mmol). The mixture was allowed to stir at 140 °C for 15 h and purification by column chromatography provided **2j** (2.0 mg) in 14% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.82 (s, 2H), 6.76 (s, 1H), 3.86 (s, 3H) 3.43 (d, *J* = 13.4 Hz, 1H), 3.37 (d, *J* = 13.4 Hz, 1H), 2.15

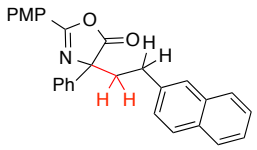
(s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.6, 137.5, 134.2, 129.9, 128.9, 128.8, 128.3, 126.0, 118.3, 114.2, 113.9, 75.7, 55.6, 47.5, 21.2; IR (film) 2925, 2853, 1813, 1727, 1655, 1608, 1512 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}NO_3$ $[M+H]^+$ *m/z* = 386.1756; found 386.1750.



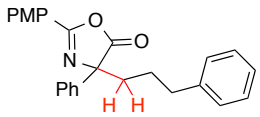
2-(4-Methoxyphenyl)-4-phenethyl-4-phenyloxazol-5(4*H*)-one (3). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in ethylbenzene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **3** (15.1 mg) in 72% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.18-7.12 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 2H), 3.90 (s, 3H), 2.66-2.58 (m, 2H), 2.56-2.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 163.5, 160.3, 140.7, 138.5, 130.2, 128.8, 128.6, 128.5, 128.3, 126.3, 125.8, 118.3, 114.4, 74.2, 55.7, 42.8, 30.8; IR (film) 3027, 2933, 1814, 1652, 1609, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ *m/z* = 371.2600; found 372.1613.

2-(4-Methoxyphenyl)-4-phenethyl-4-phenyloxazol-5(4*H*)-one (3). General procedure C was followed using **1** (15 mg, 0.056 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol), PivOH (5.7 mg, 0.056 mmol), 2,6-DMBQ (7.6 mg, 0.056 mmol) and activated carbon (13 mg, 10x weight of Pd) in ethylbenzene (137 μL, 1.12 mmol) and 1,4-dioxane (467 μL, 0.12

M) at 95 °C for 45 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **3** (14.1 mg) in 68% yield. See above for characterization.

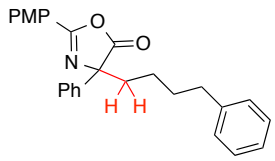


2-(4-Methoxyphenyl)-4-(2-(naphthalen-2-yl)ethyl)-4-phenyloxazol-5(4*H*)-one (4). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2-ethylnaphthalene (175 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **4** (15.3 mg) in 65% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 7.3 Hz, 1H), 7.75-7.68 (m, 4H), 7.57 (s, 1H), 7.45-7.36 (m, 4H), 7.33 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H), 2.86-2.74 (m, 2H), 2.65-2.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 163.5, 160.3, 138.5, 138.1, 133.7, 132.2, 130.2, 128.8, 128.3, 128.1, 127.7, 127.5, 127.2, 126.6, 126.1, 125.8, 125.4, 118.2, 114.4, 74.2, 56.7, 42.6, 30.9; IR (film) 3056, 2930, 1813, 1652, 1608, 1511, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{23}NO_3Na$ $[M+Na]^+$ *m/z* = 444.1576; found 444.1571.



2-(4-methoxyphenyl)-4-phenyl-4-(3-phenylpropyl)oxazol-5(4*H*)-one (5). General procedure B was followed using **1** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in propylbenzene (140 μL, 1.00 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24

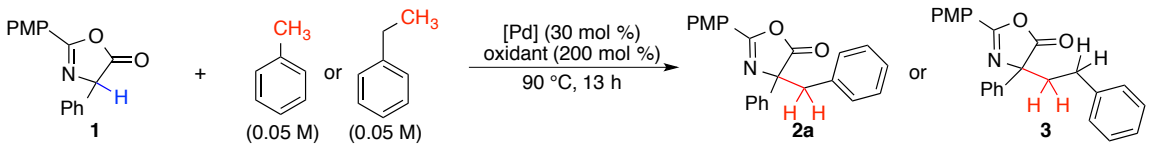
h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **5** (15.3 mg) in 62% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 9.1 Hz, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 7.7 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 2.70-2.55 (m, 2H), 2.30-2.18 (m, 2H), 1.71-1.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 163.4, 160.0, 141.6, 138.7, 130.1, 128.7, 128.5, 128.5, 128.2, 126.0, 125.8, 118.3, 114.4, 74.3, 55.7, 40.8, 35.7, 26.2; IR (film) 2952, 2933, 1815, 1653, 1601, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}NO_3$ $[M+H]^+$ *m/z* = 386.1756; found 386.1739.



2-(4-methoxyphenyl)-4-phenyl-4-(4-phenylbutyl)oxazol-5(4*H*)-one (6). General procedure B was followed using **1** (20 mg, 0.075 mmol) and $Pd(OAc)_2$ (16.9 mg, 0.075 mmol) in butylbenzene (190 μL, 1.21 mmol) and 1,4-dioxane (270 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **6** (13.8 mg) in 46% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 7.2 Hz, 2H), 7.10 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 3.89 (s, 3H), 2.55 (t, J = 7.9 Hz, 2H), 2.22 (t, J = 8.2 Hz, 2H), 1.61 (m, 2H), 1.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 163.4, 160.0, 142.4, 138.8, 130.1, 128.8, 128.4, 128.4, 128.2, 125.8, 125.8, 118.4, 114.4, 74.4, 55.7, 41.1, 35.8, 31.4, 24.1; IR (film) 2931, 2856,

1811, 1652, 1609, 1512, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{26}NO_3$ $[M+H]^+$ *m/z* = 400.1913; found 400.1913.

Table S2. PME studies with 23 oxidants and 2 Pd sources.



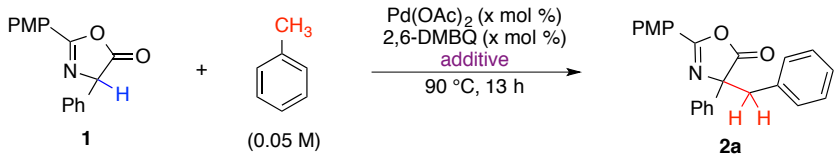
To a 96-well reactor equipped with 1 mL vials was added the indicated oxidant (Table S2, entries 1-18, 0.010 mmol, 50 μL of a 0.2 M solution in toluene) respectively. The solvent was evacuated on a Genevac. To each vial was added **1** (0.005 mmol) and the indicated Pd source (0.0015 mmol) (100 μL of a 0.05 M solution in tolyl analog). Oxidants (Table S2, entries 19-23, 0.010 mmol) were added as liquids to the respective vial. The control reactions were prepared from a solution of **1** (0.005 mmol) and Pd source (0.005 mmol) (100 μL of a 0.05 M solution in tolyl analog) into the respective vial. A parylene stir-bar was added to each vial. The reactor block was sealed, removed from the glovebox and stirred for 13 h on an Alligator tumble stirrer (1000 rpm) at 90 °C. The reactions were quenched *via* dilution with a solution of internal standard (4,4'-bis-*tert*-butyl-biphenyl) in 25% DMSO/MeCN (1.0 μmol, 0.002 M, 500 μL), and the contents were stirred for 15 minutes. Into a separate 96-well plate LC block was added 700 μL of MeCN and 25 μL of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap mat. The reaction mixtures were analyzed (P/IS and dimer/IS) using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: Acquity CORTECS BEH 1.6 μm C18; 50 mm x

2.1 mm; 1 mL/min; MeCN:H_2O:Ammonium Formate; gradient: 5% MeCN to 99% in 1.5 min, hold to 2.4 min to 5% MeCN at 2.41 min; ESC pos/neg; nebulizer: 700 L/hr; cone gas: 30 L/hr; source 150 °C; desolvation 450 °C; 210 nm: t_R of **2a** = 2.46, **3** = 2.73 and **8** = 2.73 min.

		entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Toluene	$Pd(OAc)_2$	P/IS[a]	0.0	0.0	4.5	0.0	0.0	0.8	3.1	6.7	0.9	0.0	0.0	1.9	4.5	0.0	5.8	0.7	0.0	7.4	0.0	4.8	0.0	0.0	0.9	6.9
		Dimer/IS[a]	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0
	$Pd(TFA)_2$	P/IS[a]	0.0	0.0	0.0	0.0	0.0	0.0	3.0	1.8	2.1	0.0	0.0	1.5	2.7	0.0	0.0	0.0	0.5	6.2	0.0	2.7	0.0	0.1	2.5	7.0
		Dimer/IS[a]	0.0	0.0	1.3	0.0	0.0	0.0	1.4	1.7	0.0	0.0	0.0	0.8	0.0	0.0	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	0.8
Ethylbenzene	$Pd(OAc)_2$	P/IS[a]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.1	0.0	0.0	0.0	2.1	1.6	0.0	1.7	0.0	0.0	1.6	0.5	4.5	0.0	0.4	0.0	7.1
		Dimer/IS[a]	0.0	0.0	2.1	0.0	0.7	1.0	1.8	0.0	0.0	0.0	0.0	0.9	0.0	1.0	2.7	2.8	0.7	1.0	0.0	0.8	0.0	0.0	1.6	0.0
	$Pd(TFA)_2$	P/IS[a]	0.7	0.0	0.0	0.0	0.0	0.0	1.1	0.0	0.7	0.0	0.0	1.3	0.0	0.0	0.0	0.0	1.4	4.1	0.3	2.0	0.0	1.9	0.0	4.2
		Dimer/IS[a]	0.0	0.0	1.7	0.0	0.0	0.0	1.5	2.2	0.0	0.0	0.0	1.9	0.7	1.2	2.3	0.9	0.0	0.0	0.4	0.0	0.0	1.0	2.8	0.7
Oxidant			$CuBr_2$	$CuCl_2$	$Cu(OAc)_2$	Ag_2CO_3	K_3PO_4	Ag_2O	$Ce(SO_4)_2$	$K_2S_2O_8$	F+1[b]	F+2[c]	F+3[d]	$(PhCOO)_2$	Oxone	NCS	Benzoquinone	PIDA	TBAB	2,6-DMBQ	Cumene OOH	tBuOOtBu	tBuOOH	tBuOOCOPh	DMSO	control

[a]Determined by UPLC. [b]F+1 = 1-fluoropyridinium tetrafluoroborate. [c]F+2 = 1-fluoro-2,4,6-trimethylpyridinium triflate. [d]F+3 = *N*-fluorobenzenesulfonimide.

Table S3. Optimization of catalytic benzylation.



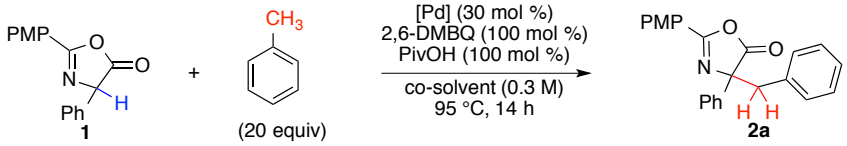
Phenylglycine azlactone **1** (10 mg, 0.038 mmol) was added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. Pd carboxylate was added, followed by 2,6-DMBQ, additive and toluene (750 μL, 0.05 M). The microwave vial was sealed with a Teflon cap, removed from the glovebox, placed in a 95 °C oil bath. After 13 h, the mixture was allowed to cool to ambient temperature, diluted

with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was analyzed by ^1H NMR and if necessary purified by column chromatography to afford **2a**. See above for characterization.

entry	additive (100 mol %)[a]	yield (%)[b]	entry	additive (100 mol %)[c]	yield (%)[b]
1	AcOH	75	4	MnO_2[c]	70
2	PivOH	84	5	AcOH, MnO_2[c]	79
3	TfOH	0	6	PivOH, MnO_2[c]	mixture[d]

[a]Pd(OAc)2 (10 mol %) and 2,6-DMBQ (100 mol %). [b]Isolated yield. [c]$Pd(OAc)_2$ (20 mol %) 2,6-DMBQ (20 mol %), MnO_2 (200 mol %). [d]50:50 mixture of P and dimer.

Table S4. PME screen of co-solvents with optimal catalytic conditions.



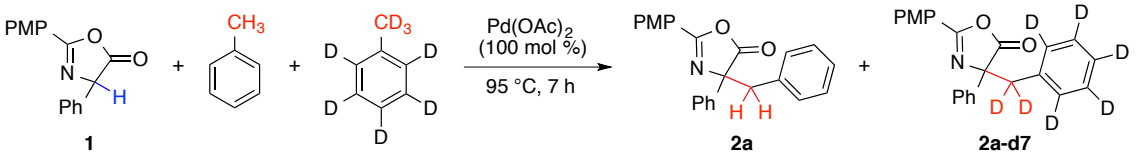
To a 24-well reactor equipped with 1 mL vials was added **1** (0.005 mmol) and 2,6-DMBQ (0.005 mmol) in THF (100 μL of a 0.05 M solution). The solvent was evacuated on a Genevac. A solution of Pd carboxylate (0.0015 mmol) and PivOH (0.005 mmol) (40 μL of a 0.038 M solution in co-solvent) was added to the 24-well reactor respectively. Toluene (22 μL, 0.1 mmol) and a parylene stir-bar were added to each vial. The reactor block was sealed, removed from the glovebox and stirred for 14 h on an Alligator tumble stirrer (1000 rpm) at 95 °C. The reactions were quenched *via* dilution with a solution of internal standard (4,4'-bis-*tert*-butyl-biphenyl) in 25% DMSO/MeCN (1.0 μmol, 0.002 M, 500 μL), and the contents were stirred for 15 minutes. Into a separate 96-well plate LC block was added 700 μL of MeCN and 25 μL of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap

mat. The reaction mixtures were analyzed (P/IS and dimer/IS) using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: Supeclco Ascentis Express C18 column 100 mm x 4.6 mm, 1.8 μm with reverse phase eluents (MeCN and 0.1 % H_3PO_4 in H_2O); 1.8 mL/min; 10 % in MeCN to 95 % MeCN in 6 min, hold for 2 min. Post time 2 min. Column at 40 °C; 210 nm: t_R of **1** = 4.7, **2a** = 5.9 and **8** = 6.5 min.

entry[a]	co-solvent (0.3 M)	P/IS[b]	(P + dimer)/IS[b]	entry[c]	co-solvent (0.3 M)	P/IS[b]	(P + dimer)/IS[b]
1	DMF	0.53	0.53	7	DMF	0.20	0.79
2	NMP	0.73	0.79	8	NMP	0.61	0.81
3	1,4-dioxane	2.24	4.26	9	1,4-dixoane	1.87	2.92
4	2-butanol	0.80	1.44	10	2-butanol	1.12	1.12
3	diglyme	0.34	2.14	11	diglyme	0.86	2.25
4	$MeCO_2i$-Pr	0.87	2.54	12	$MeCO_2i$-Pr	1.08	1.85

[a][Pd] = $Pd(OAc)_2$. [b]Determined by HPLC. [c][Pd] = $Pd(TFA)_2$.

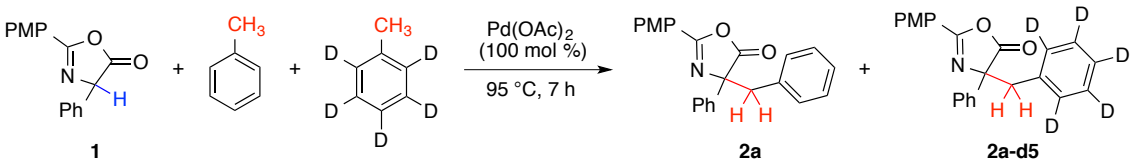
KIE Studies: d_8-toluene (Scheme 5)



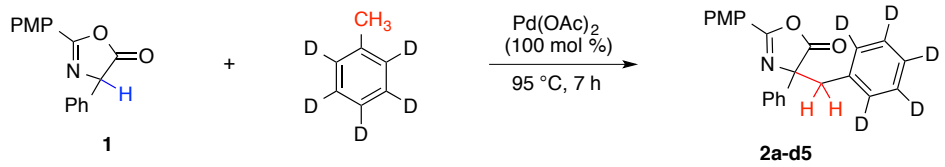
Phenylglycine azlactone **1** (10 mg, 0.038 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. $Pd(OAc)_2$ (8.4 mg, 0.038 mmol) was added followed by toluene (138 μL, 1.5 mmol) and d_8-toluene (150 μL, 1.5 mmol). The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 7 h, the mixture was allowed to cool to

ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a mixture of **2a** and **2a-d7** (12 mg) in 89% yield. Two trials were conducted and the k_H/k_D = 3.4 ± 0.15. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.22-7.11 (m, 3.8H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.51 (d, *J* = 13.4 Hz, 0.74H), 3.44 (d, *J* = 13.4 Hz, 0.77H).

KIE Studies: d_3-toluene (Scheme 5)

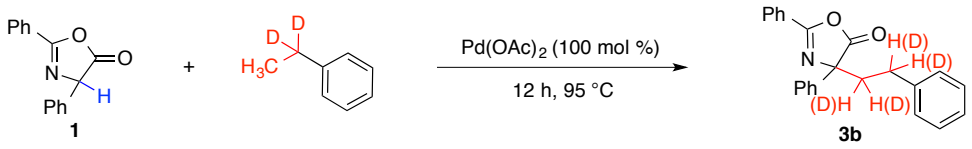


Phenylglycine azlactone **1** (27 mg, 0.1 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. $Pd(OAc)_2$ (23 mg, 0.1 mmol) was added followed by toluene (319 μL, 3.0 mmol) and d_5-toluene (336 μL, 3.0 mmol). The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 7 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a mixture of **2a** and **2a-d5** (19 mg) in 53% yield with k_H/k_D = 1.08. ^{1}H NMR (500 MHz, $CDCl_3$) 7.87 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.41-7.34 (m, 3H), 7.21-7.15 (m, 2.6H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.52 (d, *J* = 13.4 Hz, 1H), 3.45 (d, *J* = 13.4 Hz, 1H).



Phenylglycine azlactone **1** (7.0 mg, 0.026 mmol) and $Pd(OAc)_2$ (6.0 mg, 0.026 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. d_5-Toluene (200 μL, 2.0 mmol) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 7 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a mixture of **2a-d5** (9 mg) in 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H), 3.51 (d, J = 13.4 Hz, 1H), 3.44 (d, J = 13.4 Hz, 1H).

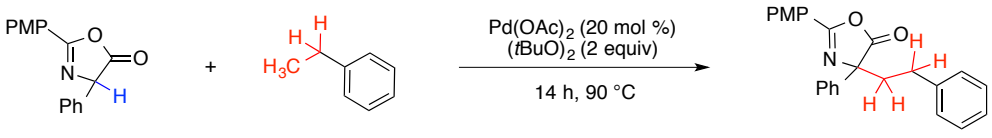
Deuterium scrambling with ethylbenzene (eq 5)



Phenylglycine azlactone **1** (10 mg, 0.038 mmol) and $Pd(OAc)_2$ (9.5 mg, 0.038 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. d_2-Ethylbenzene (700 μL, 5.7 mmol) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox

and placed in a 95 °C oil bath. After 12 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **3b** (3.1 mg) in 22% yield: ^{1}H NMR matched spectrum above for **3** but the peaks at 2.66-2.58 (m, 2H) and 2.56-2.43 (m, 2H) were observed as 2.66-2.56 (m, 0.75H) and 2.56-2.43 (m, 1.24H) corresponding to 38% and 62% H incorporation respectively. This experiment was repeated with general procedure B and the ^{1}H NMR matched spectrum above for **3** but the peaks at 2.66-2.58 (m, 2H) and 2.56-2.43 (m, 2H) were observed as 2.66-2.56 (m, 0.8H) and 2.56-2.43 (m, 1.4H) corresponding to 40% and 70% H incorporation respectively.

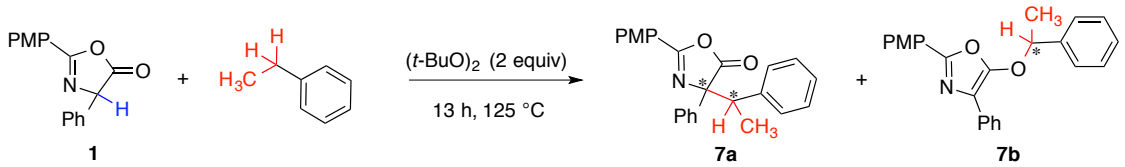
Radical studies with ethylbenzene (Table 2)



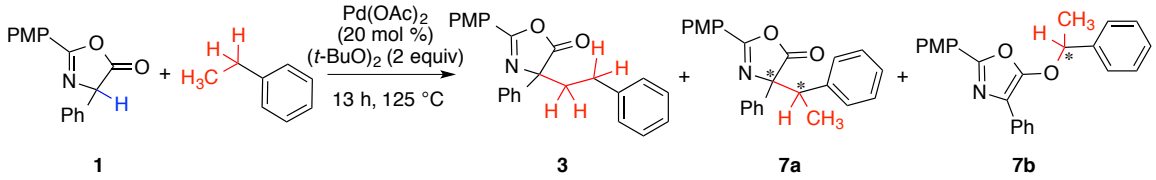
1 **3**

Phenylglycine azlactone **1** (11.2 mg, 0.042 mmol) and $Pd(OAc)_2$ (1.9 mg, 0.008 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar, and brought into the glovebox. A solution of di-*tert*-butylperoxide (*t*-BuO)$_2$ in ethylbenzene (855 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 90 °C oil bath. After 14 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was

purified by column chromatography (7% EtOAc in hexanes) to afford **3** (5.9 mg) in 38% yield. The remaining product was phenylglycine azlactone dimer. See above for characterization.



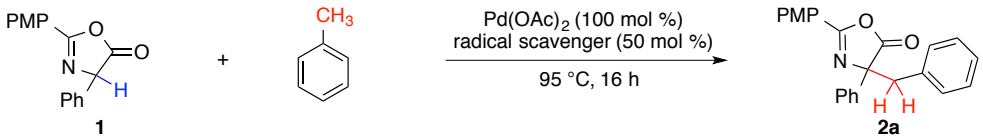
Phenylglycine azlactone **1** (60 mg, 0.23 mmol) was added to a flame dried 8 mL microwave vial equipped with a stirbar, and brought into the glovebox. A solution of (*t*-BuO)$_2$ in ethylbenzene (4.58 mL, 0.1 M) was added. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 125 °C oil bath. After 13 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (2 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (15% EtOAc in hexanes) to afford a 9:1 inseperable mixture of **7a** and **7b** (50 mg) in 60% yield. This mixture which consisted of six isomers of **7a** and **7b** was further analyzed in a collaboration with Erik Regalado and Christopher Welch at Merck Research Laboratories, Rahway, NJ.[2]



Phenylglycine azlactone **1** (11.2 mg, 0.042 mmol) and Pd(OAc)$_2$ (1.9 mg, 0.008 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar, and brought into the glovebox. A solution of (*t*-BuO)$_2$ in ethylbenzene (855 μL, 0.1 M) was

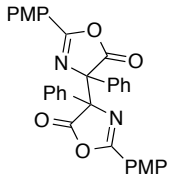
added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 125 °C oil bath. After 13 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a 1:8:1 mixture of **3**, **7a**, and **7b**.

Table S5. Radical scavengers study.



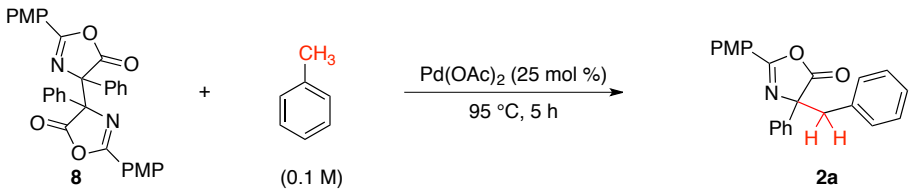
Phenylglycine azlactone **1** (10 mg, 0.037 mmol) and radical scavenger (0.019 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) was added followed by toluene (370 μL, 3.7 mmol). The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 16 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **2a**. See above for characterization.

entry	radical scavenger (50 mol %)	yield (%)	recovered scavenger (%)
1	TEMPO	54	0
2	1,1-diphenylethylene	85	58
3	BHT	59	67
4	none	83	-



2,2'-bis(4-methoxyphenyl)-4,4'-diphenyl-[4,4'-bioxazole]-5,5'(4*H*,4'*H*)-dione (8). Phenylglycine azlactone **1** (60 mg, 0.23 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and Ag_2O (52 mg, 0.23 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar and brought into the glovebox. Toluene (2.3 mL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and allowed to stir at ambient temperature. After 5 h, the mixture was purified directly by column chromatography (20% EtOAc in hexanes) to afford **8** (50 mg) in 83% yield as a white solid. A single crystal for X-ray structural analysis was obtained by slow-evaporation from CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ major: 7.88 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.20 (m, 3H), 6.85 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H); minor: 7.9.4 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H), 7.30 (m, 3H), 6.90 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H). Spectral data matched those reported previously by Marquez.[3]

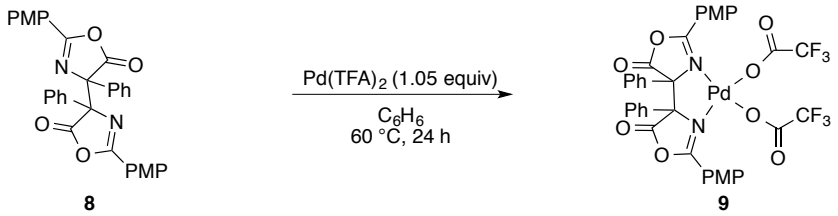
Dimer with catalytic Pd (Scheme 6)



Phenylglycine azlactone dimer **8** (10.0 mg, 0.019 mmol) and $Pd(OAc)_2$ (1.1 mg, 0.0049 mmol) were added to a flame dried 8 mL microwave vial equipped with a stirbar,

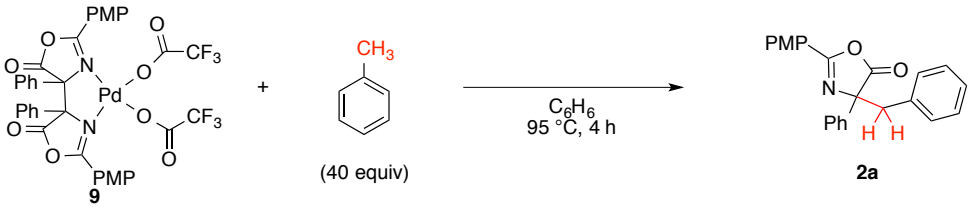
and brought into the glovebox. Toluene (375 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 5 h, the mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), passed through SiO_2 with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **2a** (9.5 mg) in 72% yield. See above for characterization.

Dimer with $Pd(TFA)_2$ complex (Scheme 6)



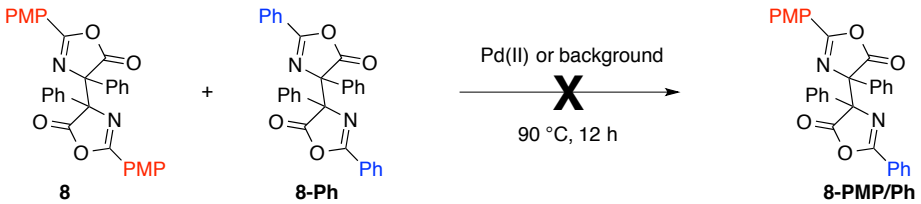
Phenylglycine azlactone dimer **8** (25 mg, 0.047 mmol) and $Pd(TFA)_2$ (17.4 mg, 0.0052 mmol) were added to an NMR tube equipped with a J Young valve. The reaction mixture was put under argon and C_6D_6 (524 μL, 0.1 M), that had been sparged with argon, was added. The NMR tube was sealed and placed in a 60 °C oil bath. After 24 h, the mixture was allowed to cool to ambient temperature, the reaction mixture was decanted from the black precipitate formed during heating and concentrated *in vacuo*. A single crystal for X-ray structural analysis was obtained by dissolving the resulting residue in THF, layering hexanes on top and storing the mixture in a -8 °C freezer overnight. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, J = 7.9 Hz, 2H), 7.94 (d, J = 9.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 6.90 (t, J = 7.5 Hz, 1H), 6.41 (d, J = 9.2 Hz, 2H), 3.00 (s, 3H).

Dimer-Pd complex with toluene (Scheme 6)



Phenylglycine azlactone dimer **9** (8 mg, 0.015 mmol) and $Pd(TFA)_2$ (5.5 mg, 0.017 mmol) were added to an NMR tube equipped with a J Young valve. The reaction mixture was put under argon and C_6D_6 (524 μL, 0.1 M), that had been sparged with argon, was added. The NMR tube was sealed and placed in a 60 °C oil bath. After 24 h, the mixture was allowed to cool to ambient temperature, toluene (165 μL, 0.1 M) was added and the mixture was placed in a 95 °C oil bath. After 4 h, the mixture was allowed to cool to ambient temperature and purified directly by column chromatography (7% EtOAc in hexanes) to afford **2a** (4.0 mg) in 37% yield. See above for characterization.

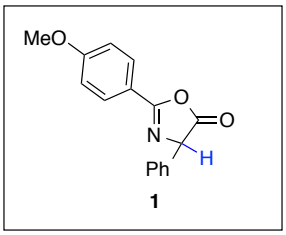
Scheme S1. Dimer crossover experiment.



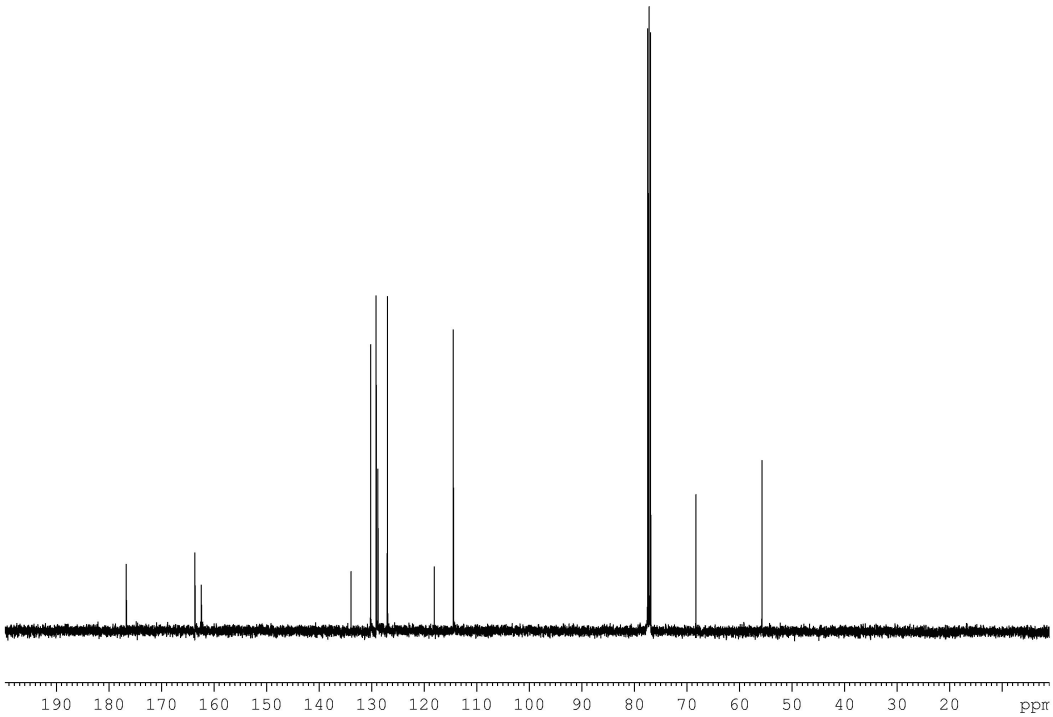
Phenylglycine azlactone dimer **8** (6.3 mg, 0.012 mmol), phenylglycine azlactone dimer **8-Ph** (5.6 mg, 0.012 mmol) and additive [$Pd(OAc)_2$ (5.4 mg, 0.024 mmol) or no additive] was added to a flame dried 8 mL microwave vial equipped with stir bar, and brought into the glovebox. To each mixture, benzene (240 μL, 0.1 M) was added. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in an 90 °C oil bath. After 12 h, each mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (1 mL), purified directly by column chromatography (15% EtOAc in hexanes) to afford only recovered **8** and **8-Ph**. Analysis by UPLC MS suggested dimer mixing but further investigation with a control (**8** and **8-Ph** mixed together at rt and analyzed) revealed ionization causes mixing during the MS analysis.

References:

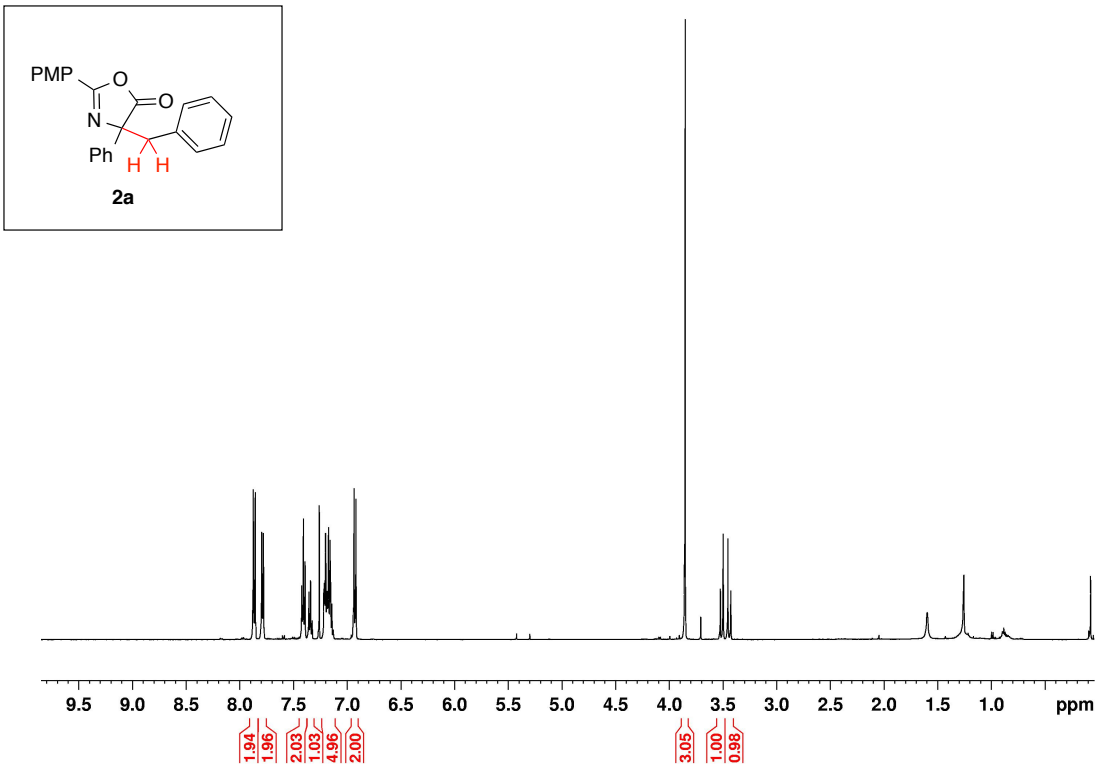
1) $Au(OAc)_3$, $Cu(OAc)_2$, $Rh_2(OAc)_4$ and $Ni(OAc)_2$ were avaialble from commercial sources. $[Pt_4(OAc)_8]$•HOAc was synthesized following a known procedure, see: Basato, M.; Biffis, A.; Martinati, G.; Tubaro, C.; Venzo, A.; Ganis, P.; Benetolo, F. *Inorg. Chim. Acta* **2003**, *355*, 399.
2) Regalado, E. L.; Kozlowski, M. C.; Curto, J. M.; Ritter, T.; Campbell, M. G.; Mazzotti, A. R.; Hamper, B. C.; Spilling, C. D.; Mannino, M. P.; Wan, L.; Yu, J.-Q.; Liu, J.; Welch, C. J. *Org. Biomol. Chem.* **2014**, *12*, 2161.
3) Rodriguez, H.; Marquez, A.; Chuaqui, C. A.; Gomez, B. *Tetrahedron* **1991**, *47*, 5681.



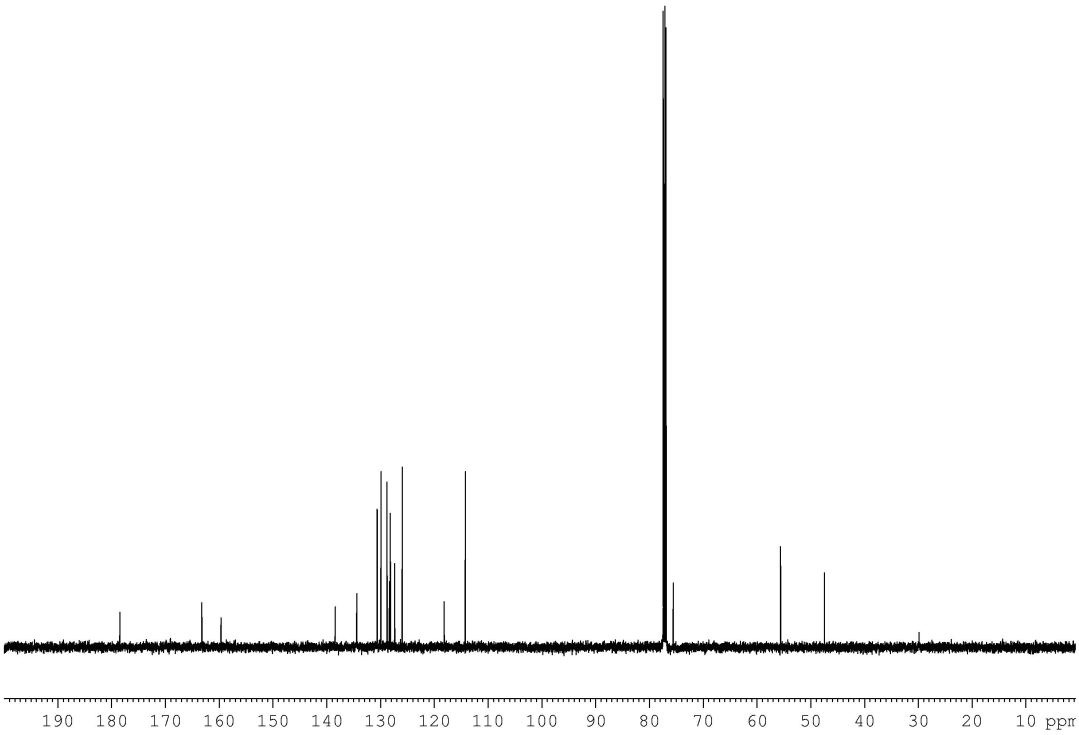
^{1}H NMR spectrum of compound **1** (500 MHz, $CDCl_3$)



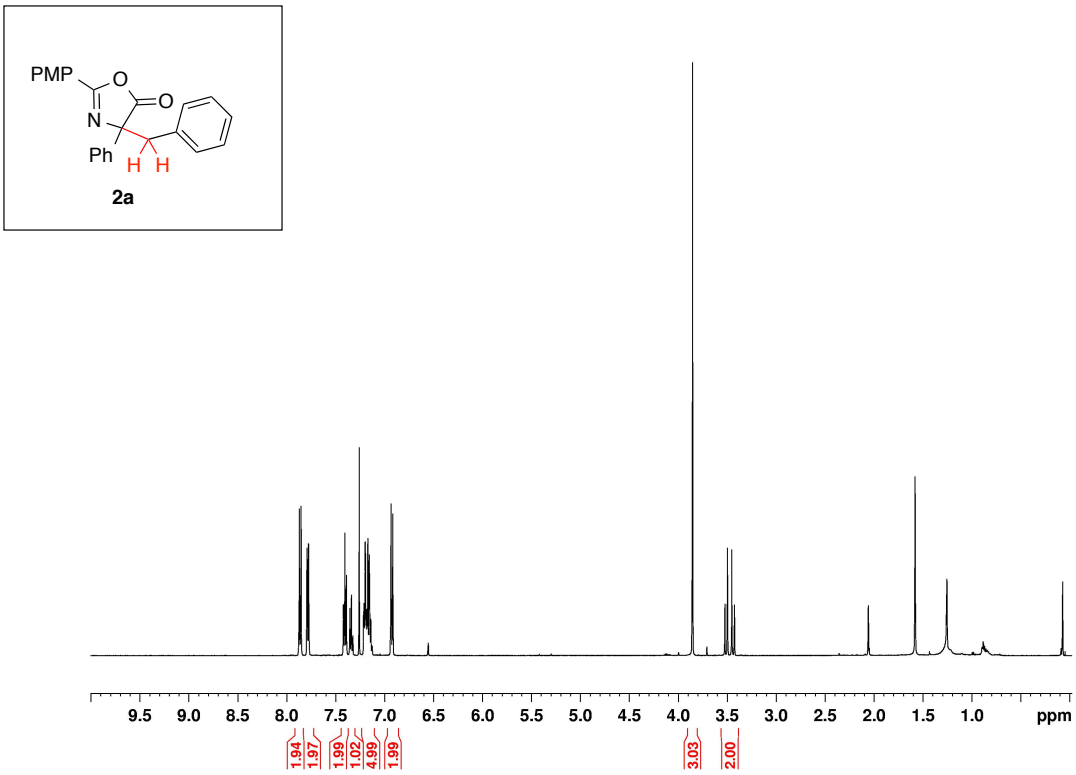
^{13}C NMR spectrum of compound **1** (125 MHz, $CDCl_3$)



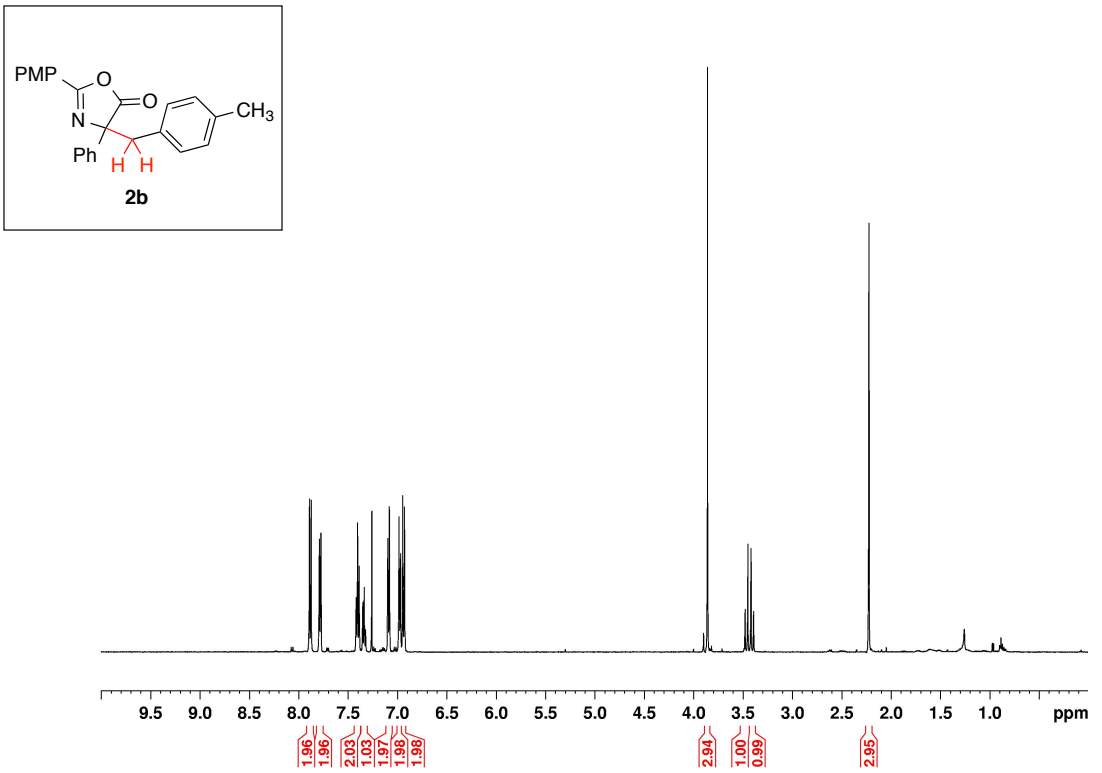
Scheme 2. ^{1}H NMR spectrum of compound **2a** (500 MHz, $CDCl_3$)



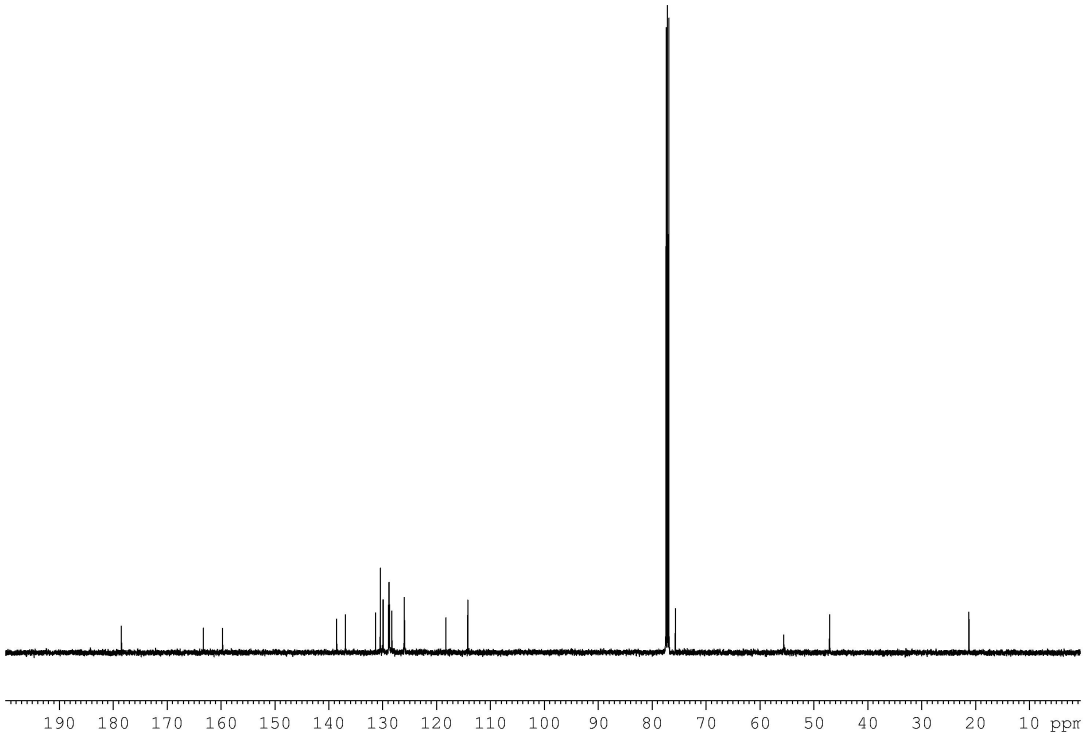
Scheme 2 ^{13}C NMR spectrum of compound **2a** (125 MHz, $CDCl_3$)



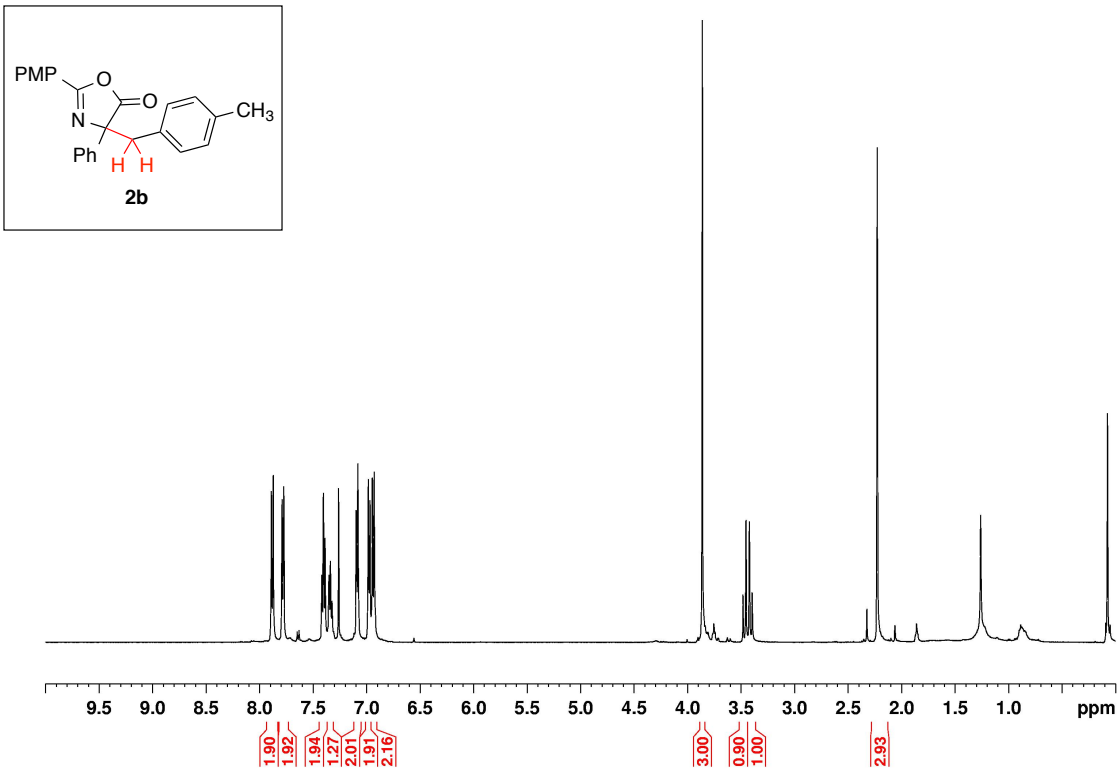
Scheme 4. ^{1}H NMR spectrum of compound **2a** (500 MHz, $CDCl_3$)



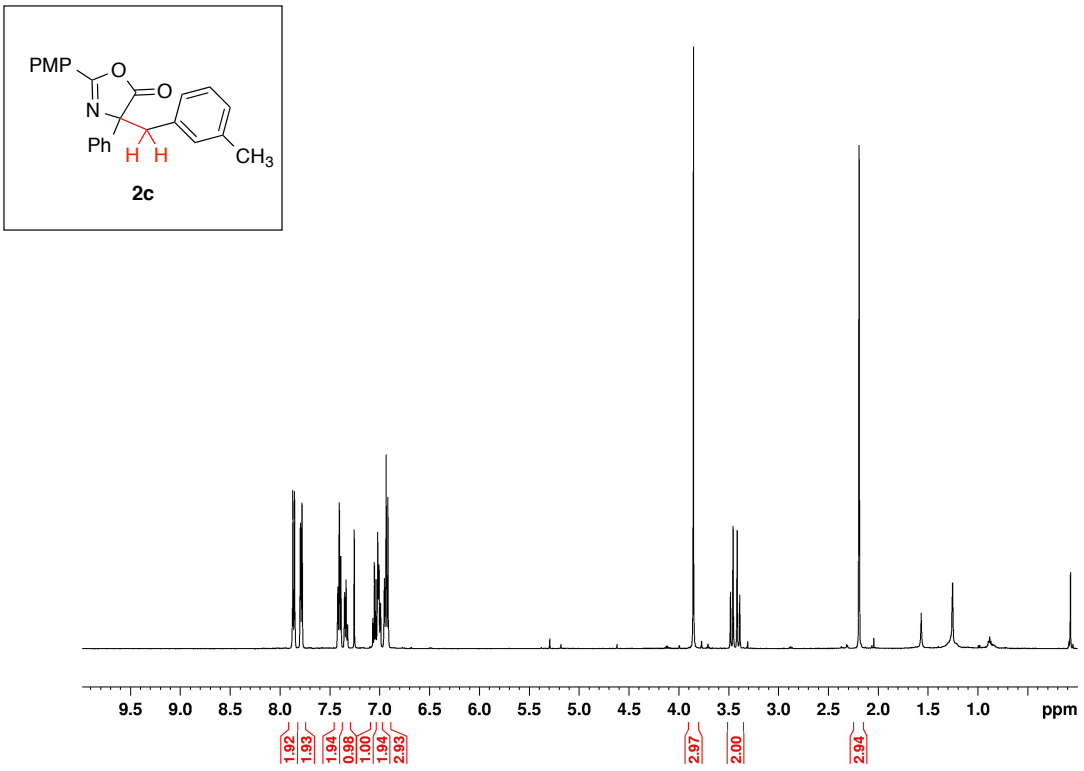
Scheme 2. ^{1}H NMR spectrum of compound **2b** (500 MHz, $CDCl_3$)



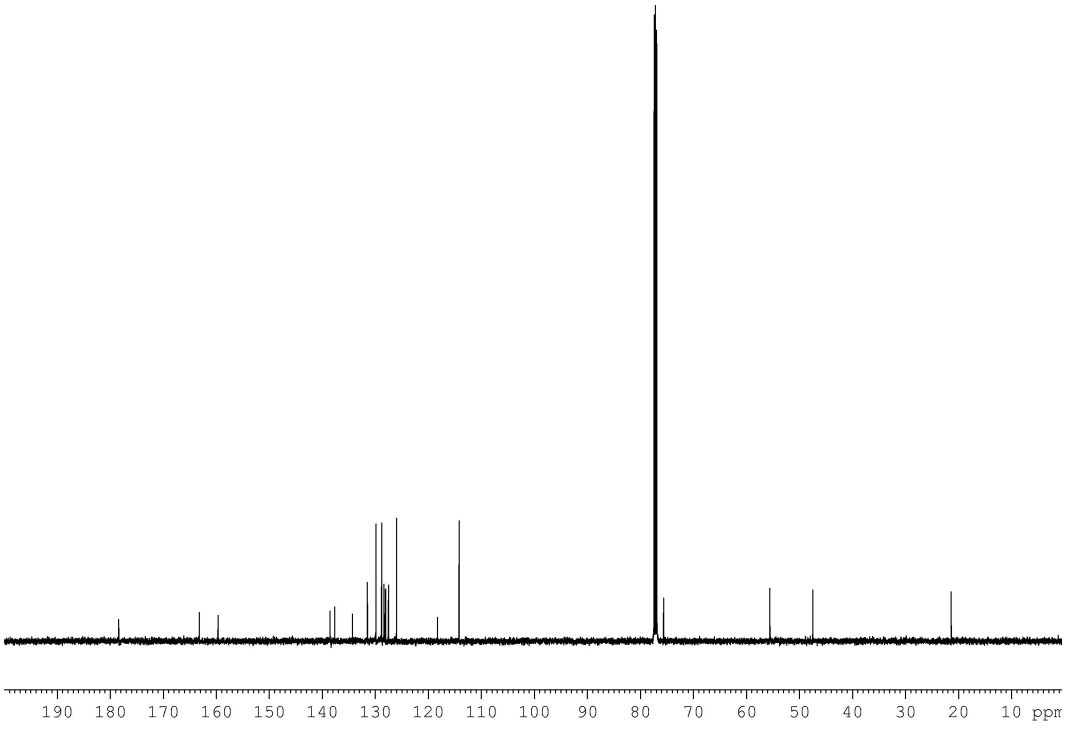
Scheme 2. ^{13}C NMR spectrum of compound **2b** (125 MHz, $CDCl_3$)



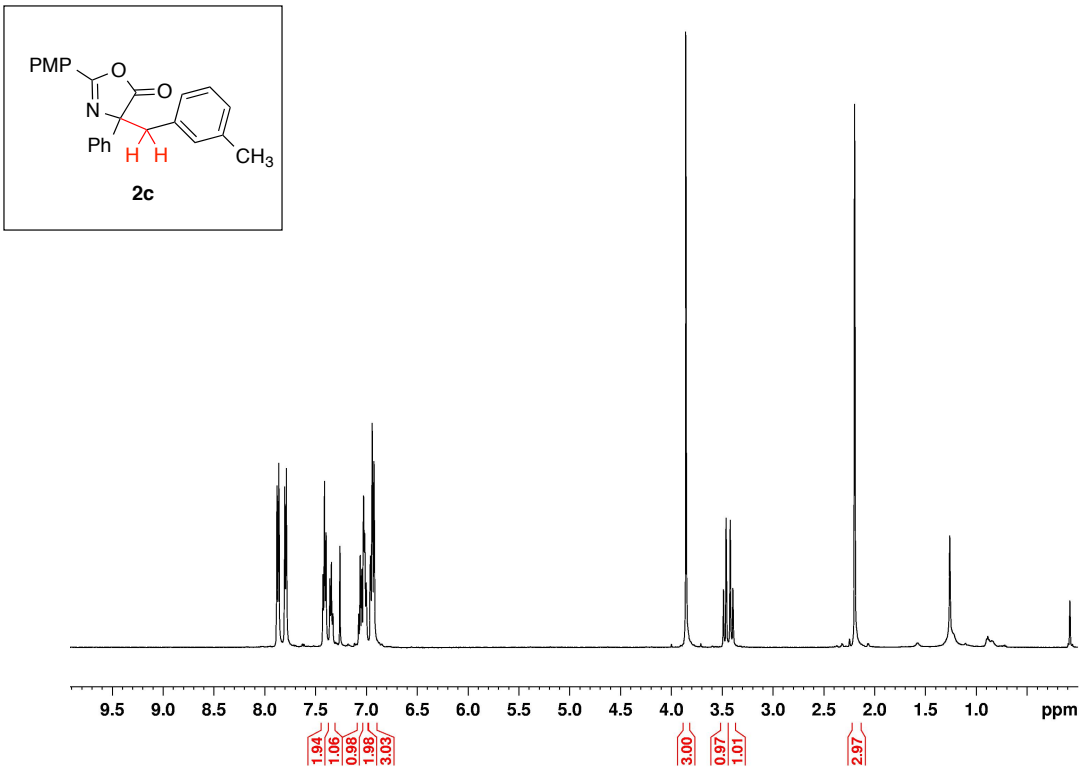
Scheme 4. ^{1}H NMR spectrum of compound **2b** (500 MHz, $CDCl_3$)



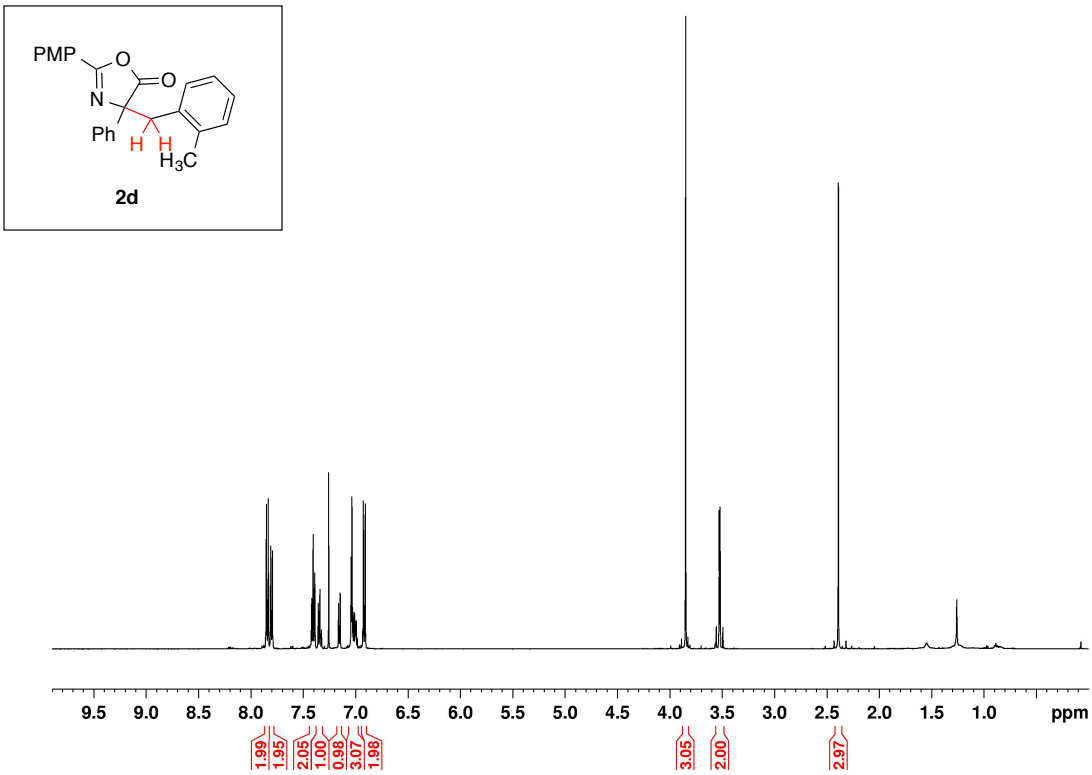
Scheme 2. ^{1}H NMR spectrum of compound **2c** (500 MHz, $CDCl_3$)



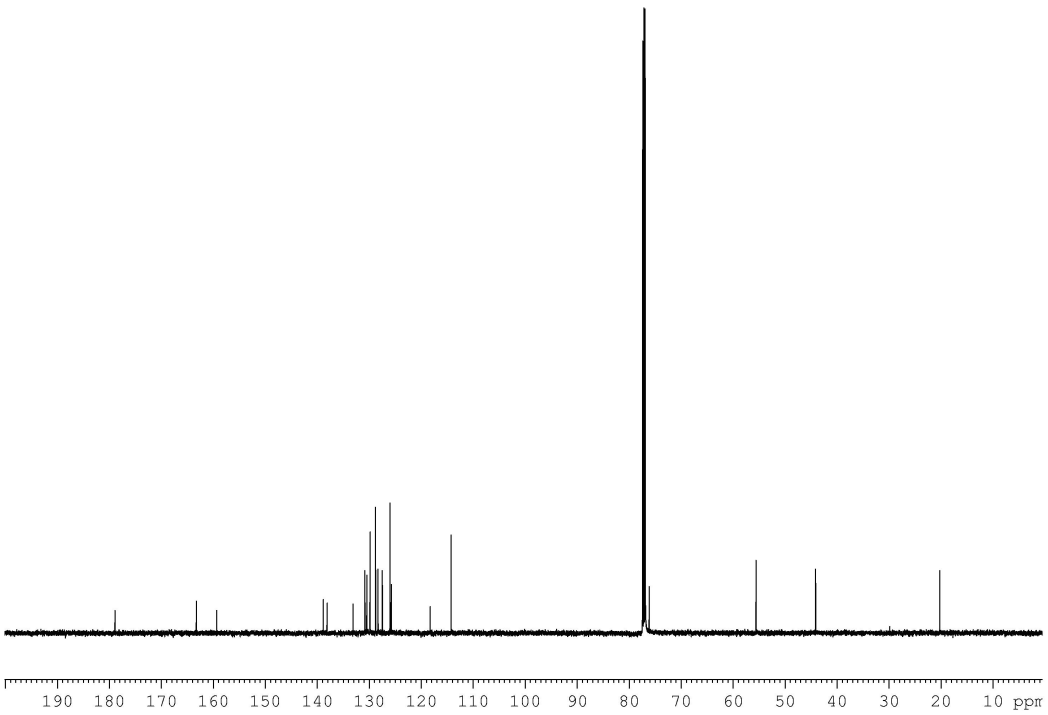
Scheme 2. ^{13}C NMR spectrum of compound **2c** (125 MHz, $CDCl_3$)



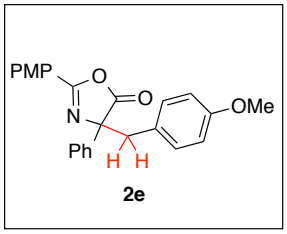
Scheme 4. ^{1}H NMR spectrum of compound **2c** (500 MHz, $CDCl_3$)



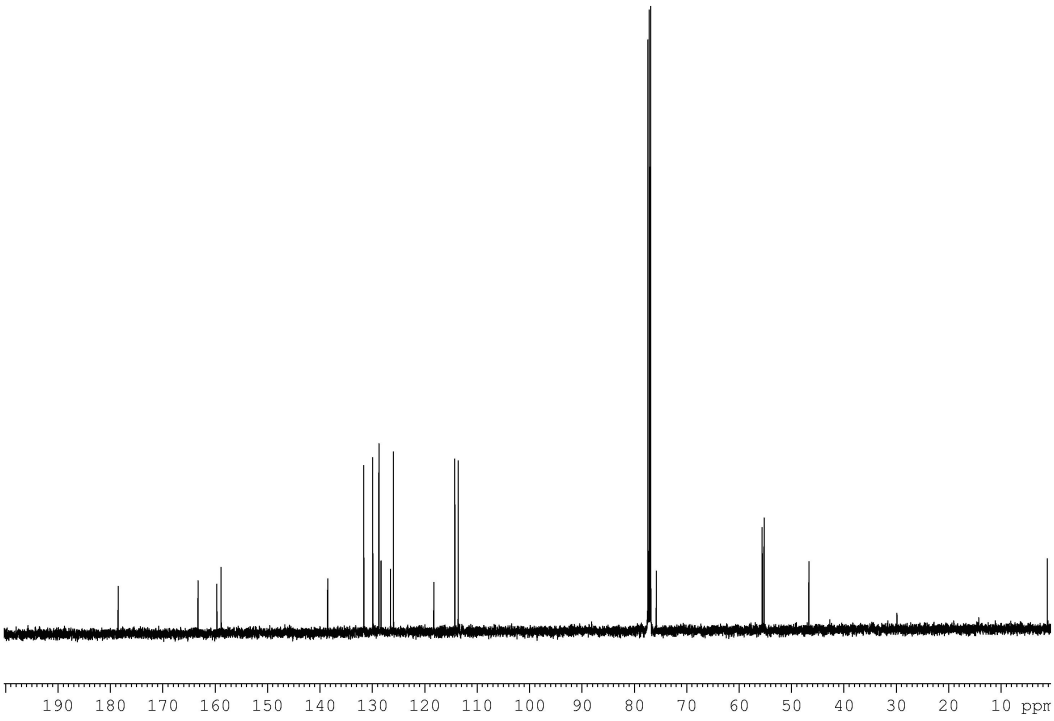
Scheme 2. ^{1}H NMR spectrum of compound **2d** (500 MHz, $CDCl_3$)



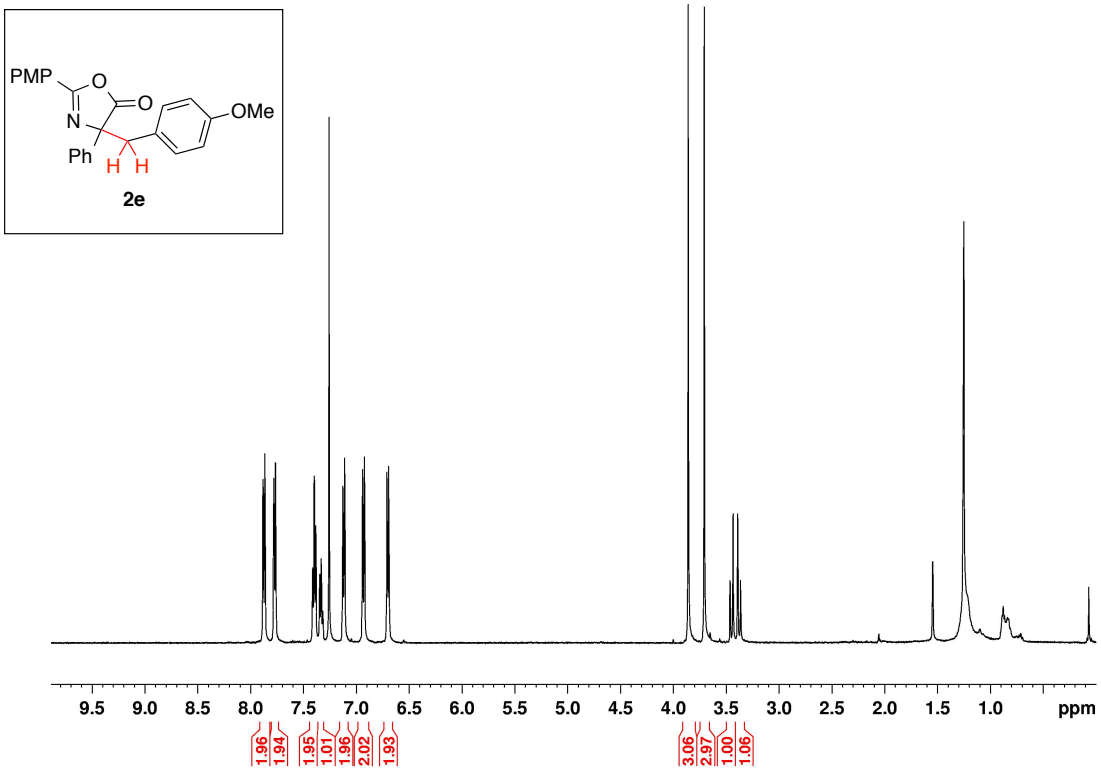
Scheme 2. ^{13}C NMR spectrum of compound **2d** (125 MHz, $CDCl_3$)



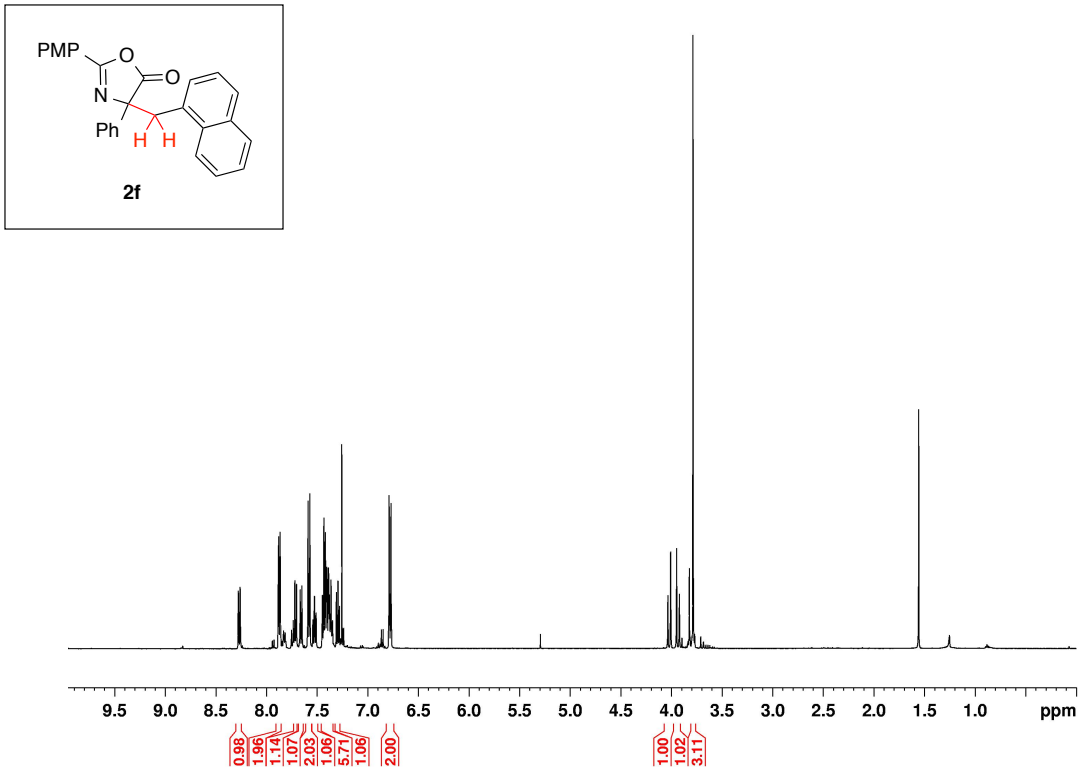
Scheme 2. ^{1}H NMR spectrum of compound **2e** (500 MHz, $CDCl_3$)



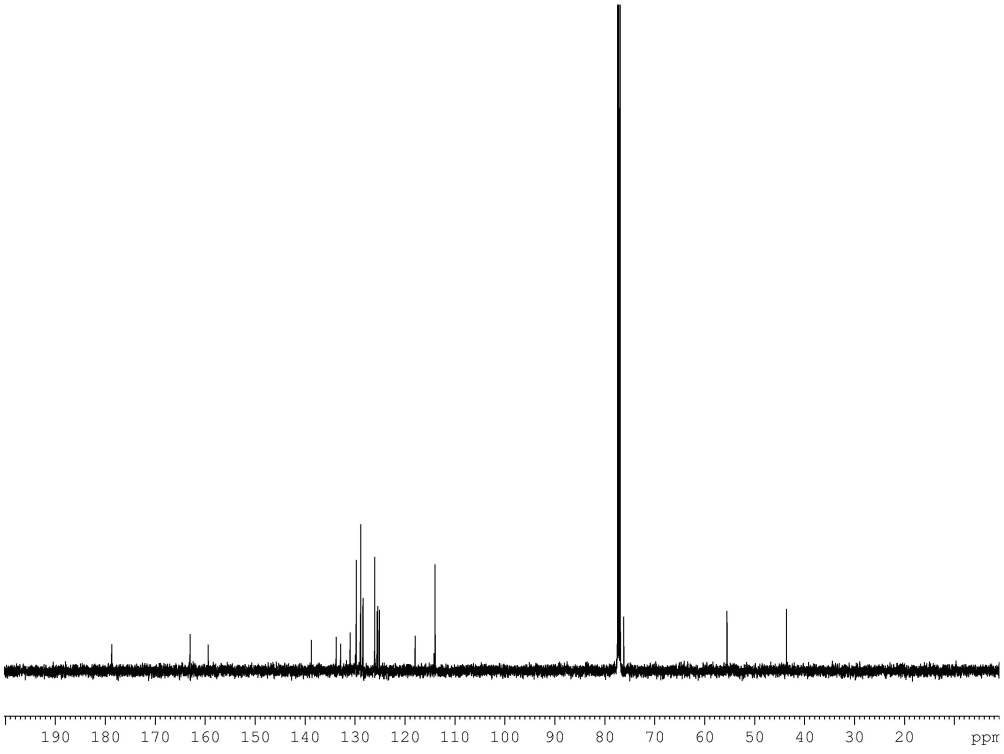
Scheme 2. ^{13}C NMR spectrum of compound **2e** (125 MHz, $CDCl_3$)



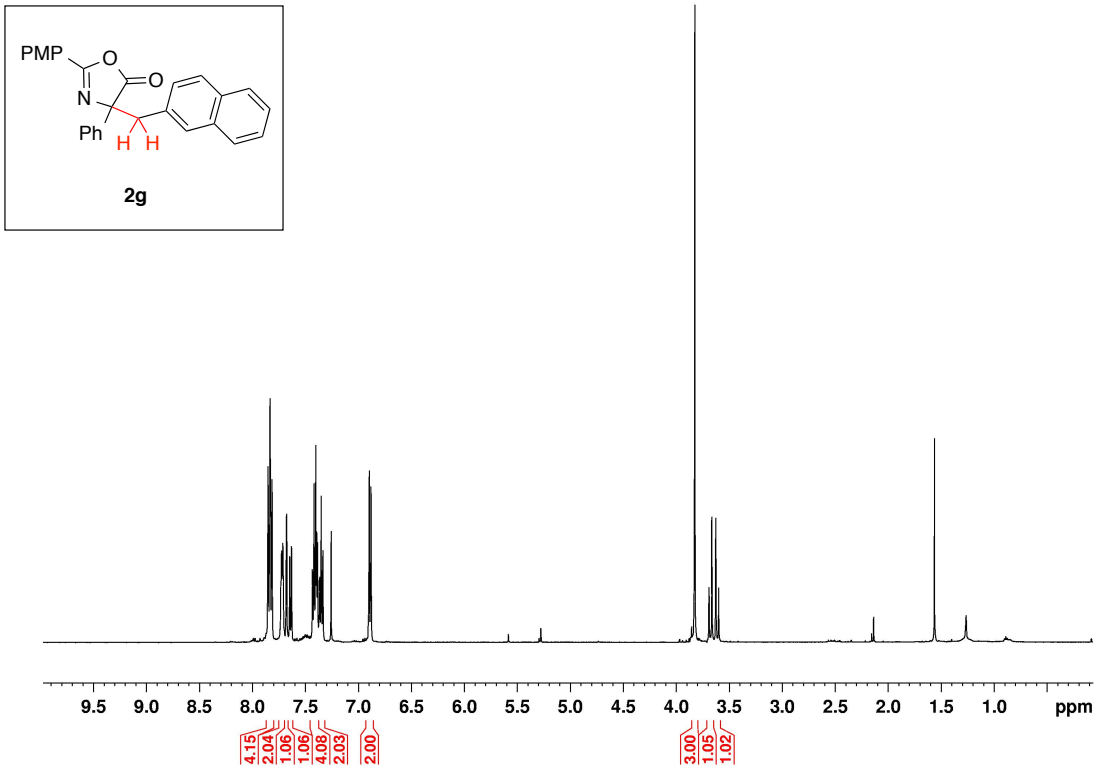
Scheme 4. ^{1}H NMR spectrum of compound **2e** (500 MHz, $CDCl_3$)



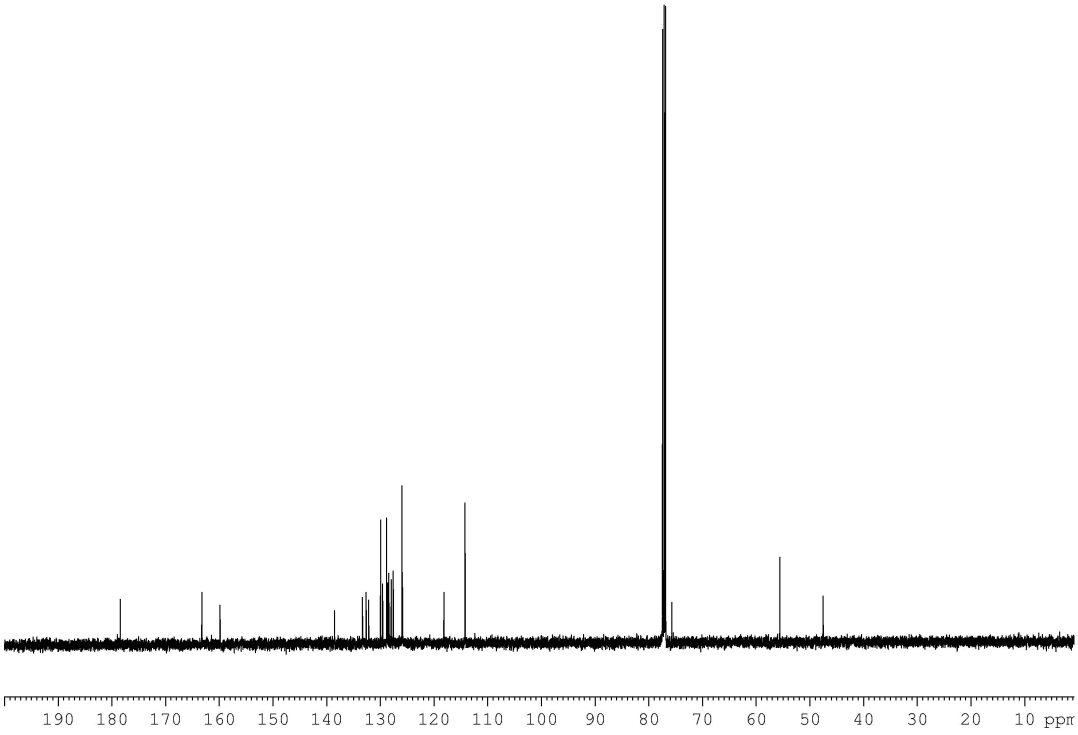
Scheme 2. ^{1}H NMR spectrum of compound **2f** (500 MHz, $CDCl_3$)



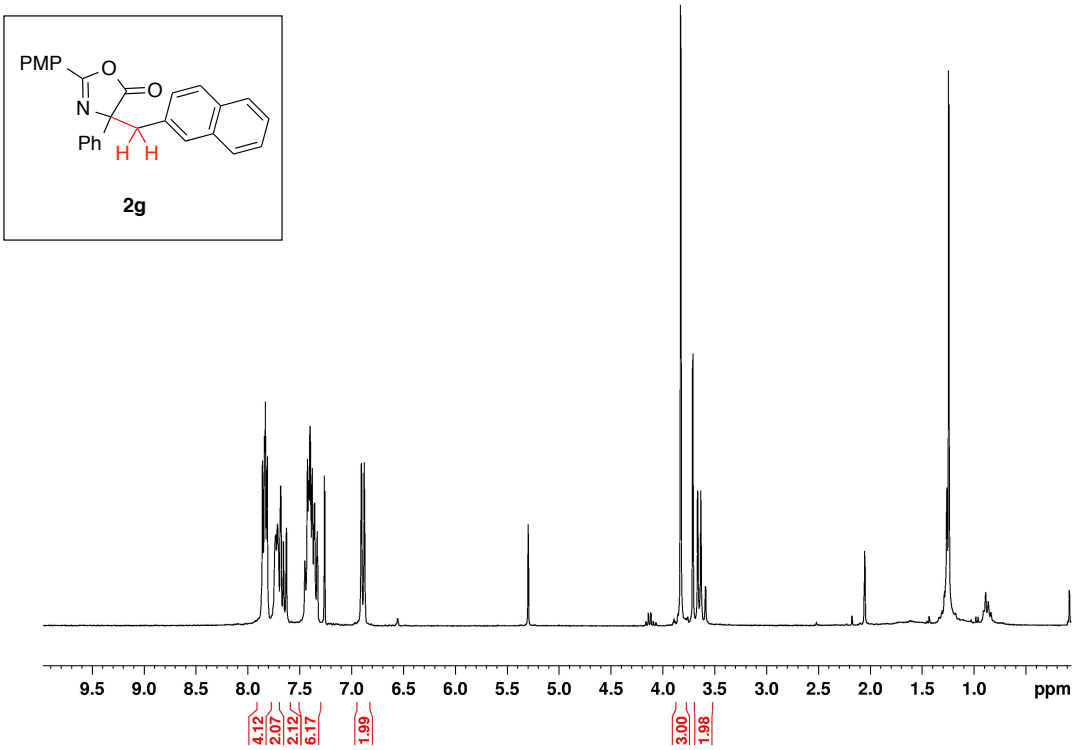
Scheme 2. ^{13}C NMR spectrum of compound **2f** (125 MHz, $CDCl_3$)



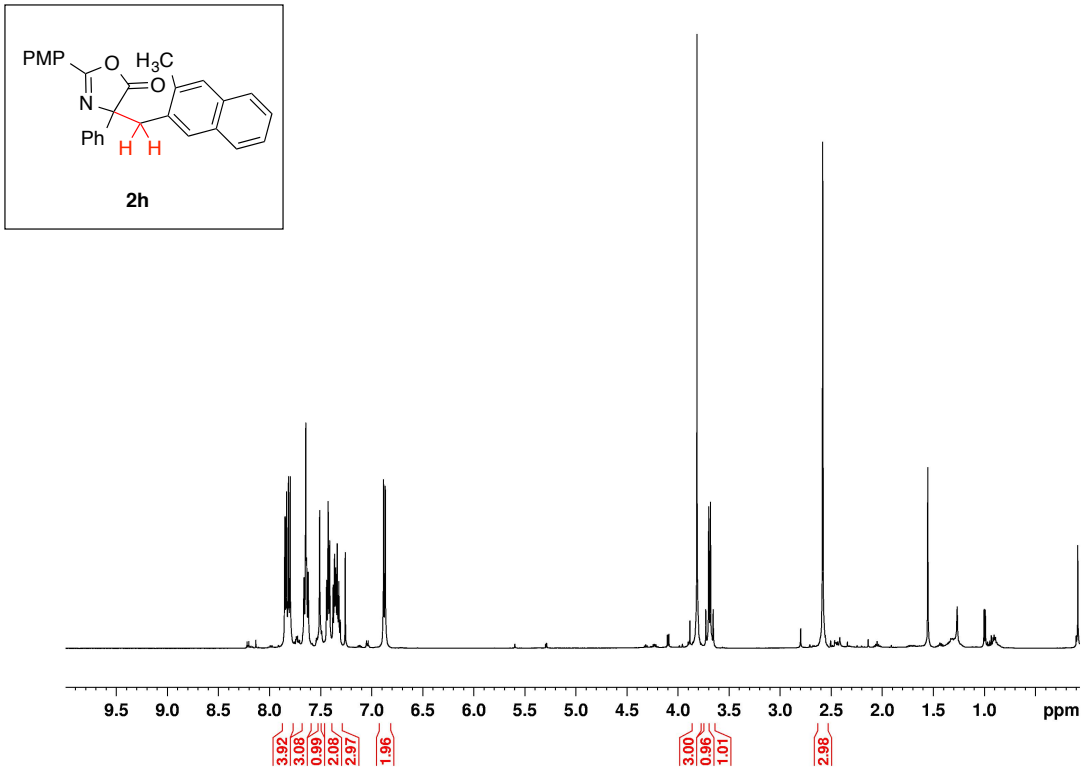
Scheme 2. ^{1}H NMR spectrum of compound **2g** (500 MHz, $CDCl_3$)



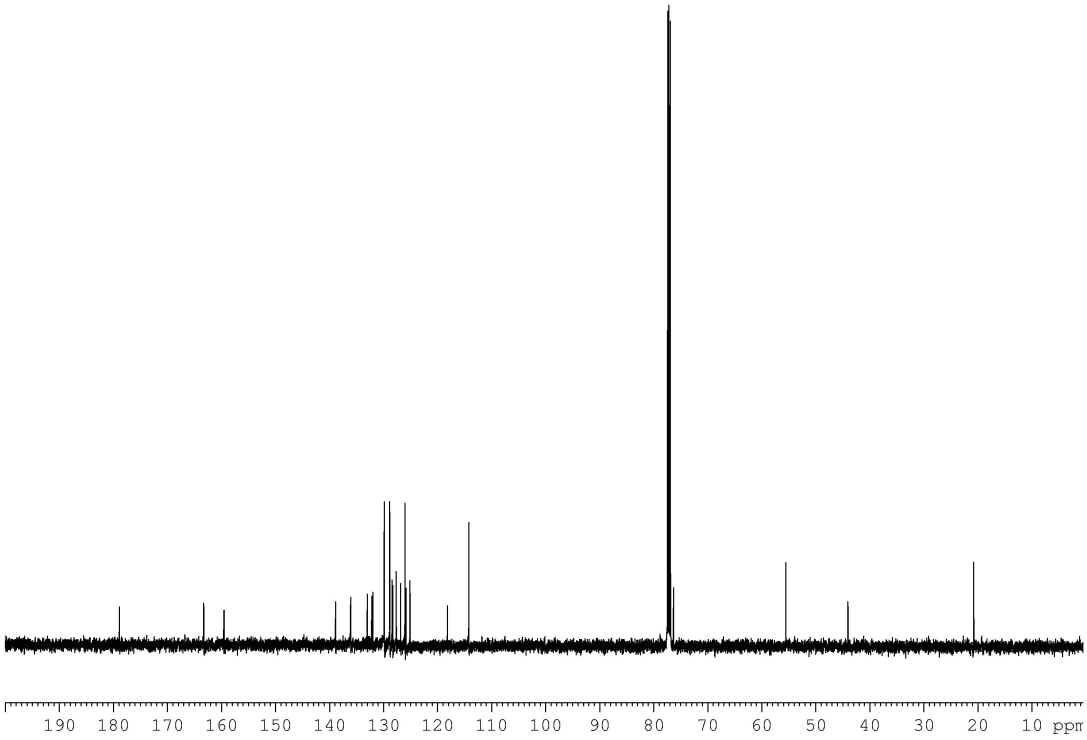
Scheme 2. ^{13}C NMR spectrum of compound **2g** (125 MHz, $CDCl_3$)



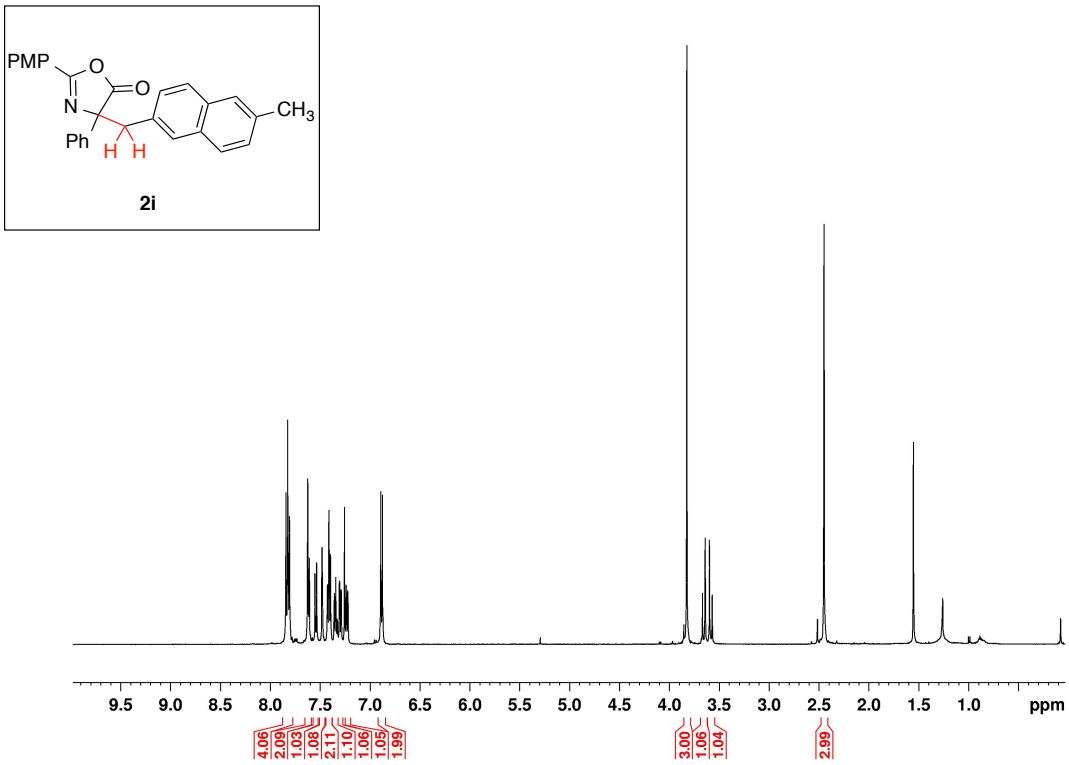
Scheme 4. ^{1}H NMR spectrum of compound **2g** (500 MHz, $CDCl_3$)



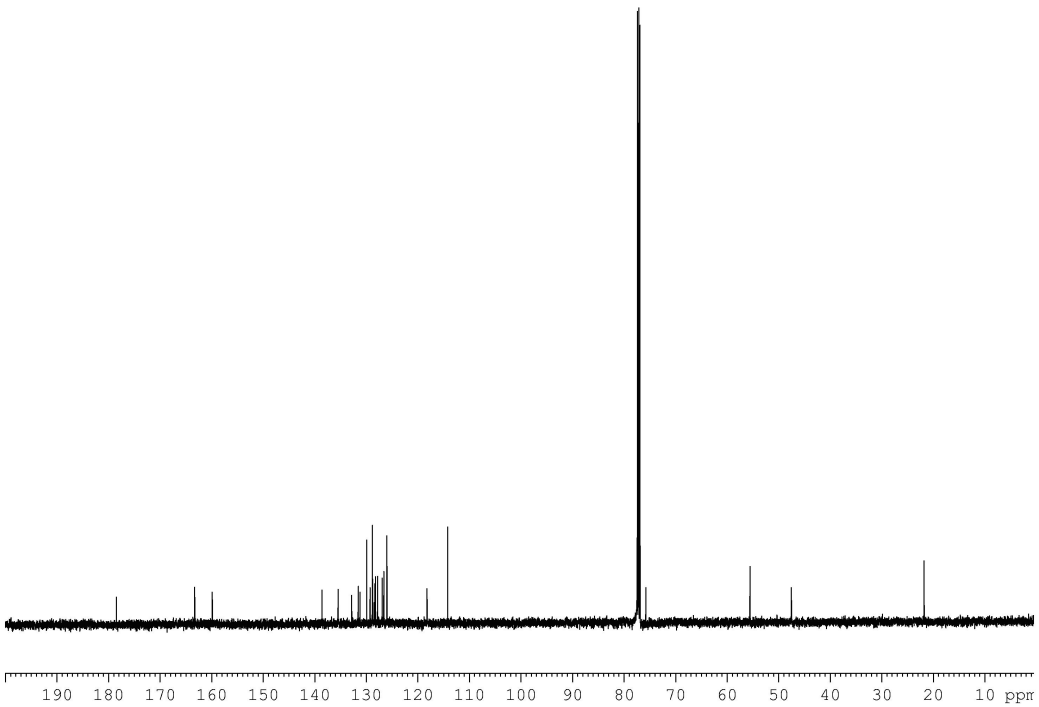
Scheme 2. ^{1}H NMR spectrum of compound **2h** (500 MHz, $CDCl_3$)



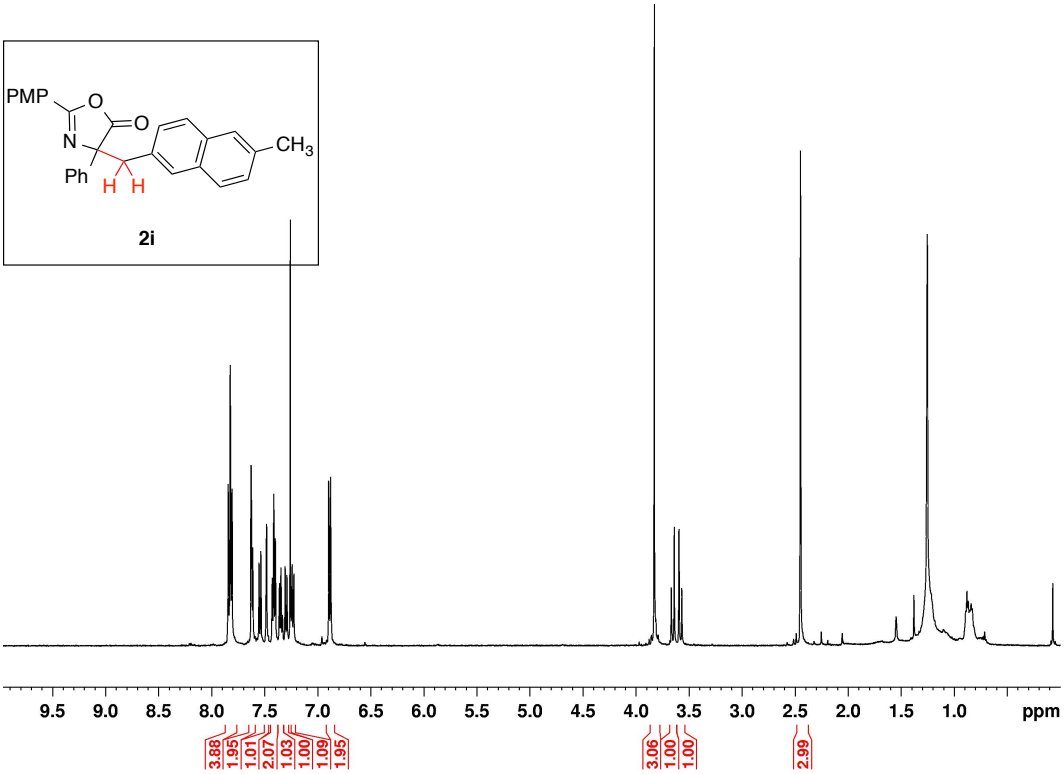
Scheme 2. ^{13}C NMR spectrum of compound **2h** (125 MHz, $CDCl_3$)



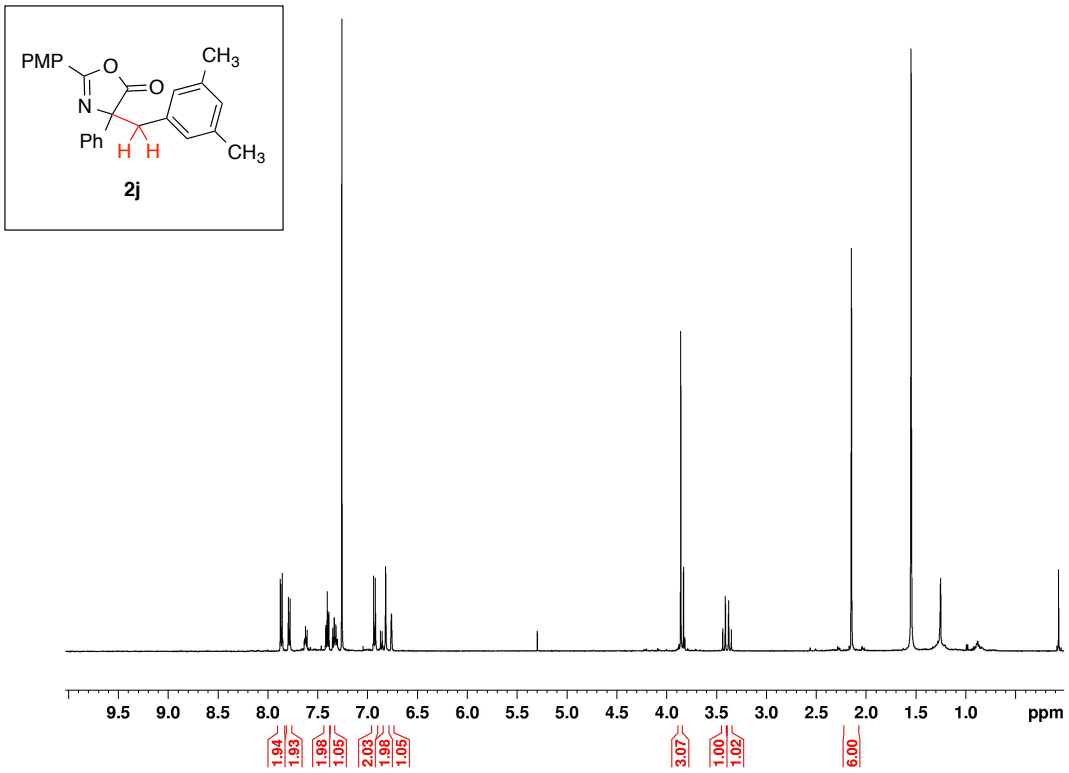
Scheme 2. ^{1}H NMR spectrum of compound **2i** (500 MHz, $CDCl_3$)



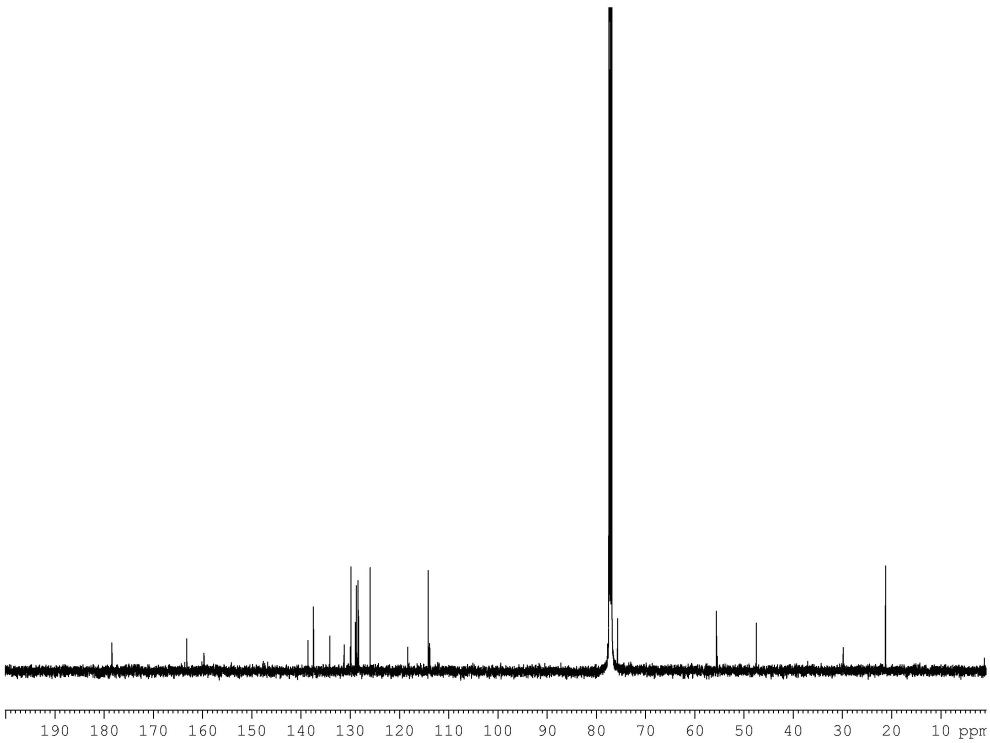
Scheme 2. ^{13}C NMR spectrum of compound **2i** (125 MHz, $CDCl_3$)



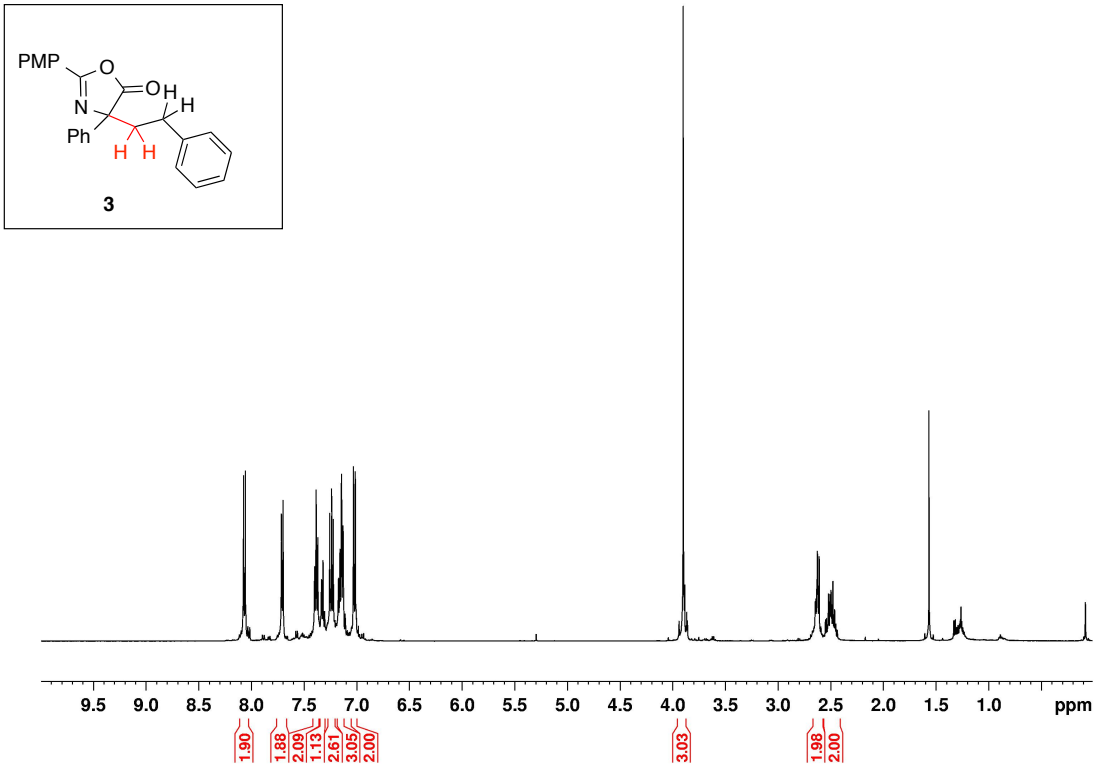
Scheme 4. ^{1}H NMR spectrum of compound **2i** (500 MHz, $CDCl_3$)



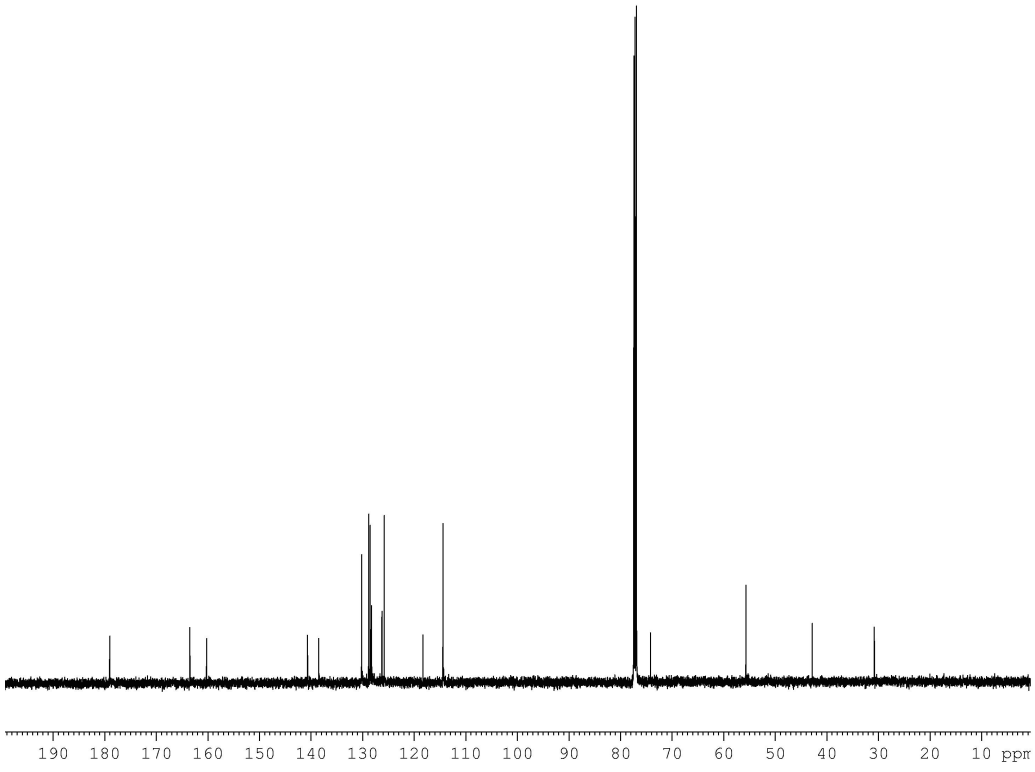
^{1}H NMR spectrum of compound **2j** (500 MHz, $CDCl_3$)



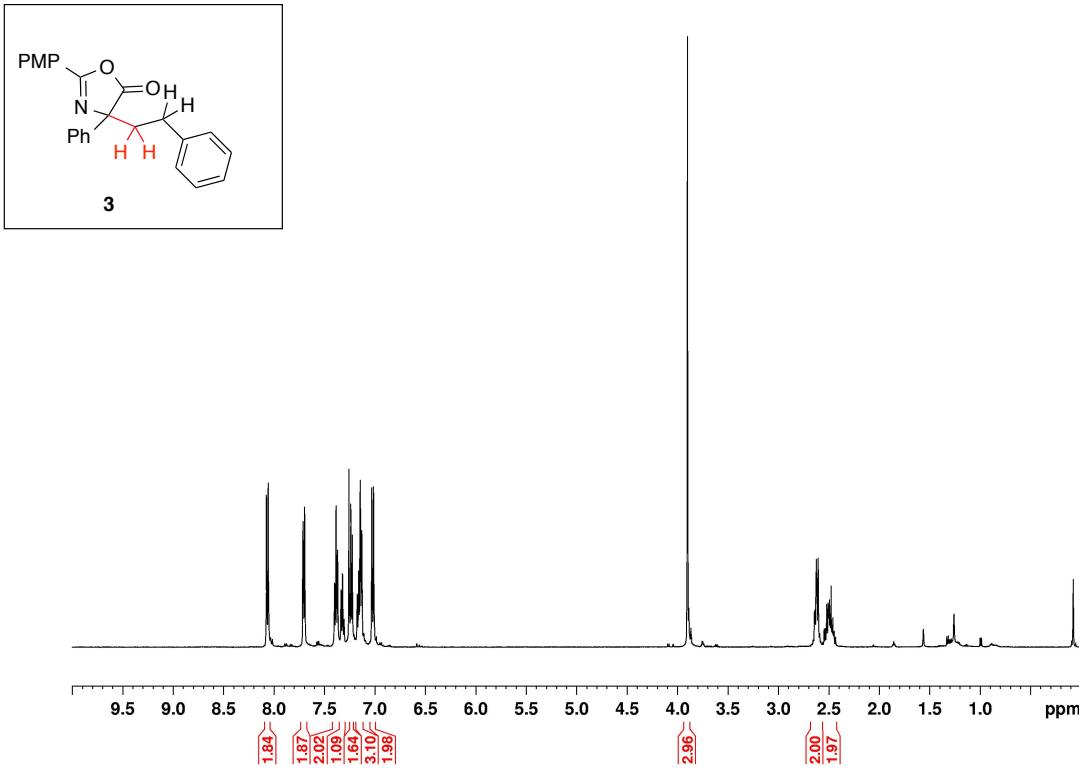
^{13}C NMR spectrum of compound **2j** (125 MHz, $CDCl_3$)



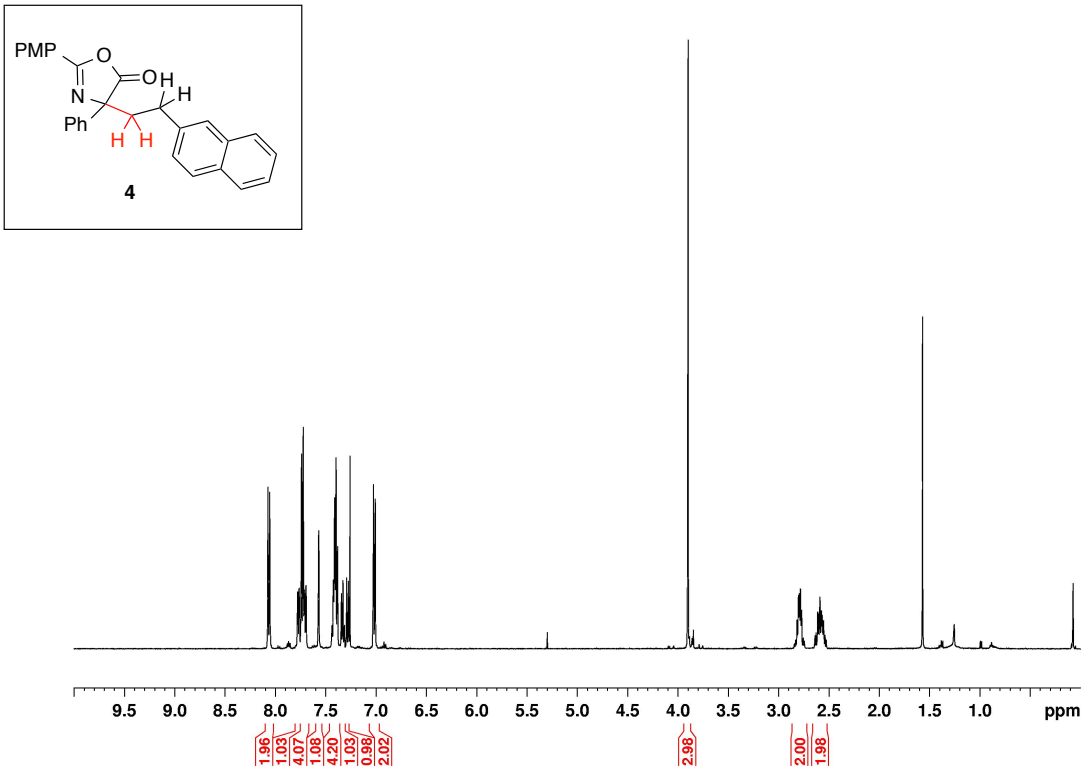
Scheme 3. ^{1}H NMR spectrum of compound **3** (500 MHz, $CDCl_3$)



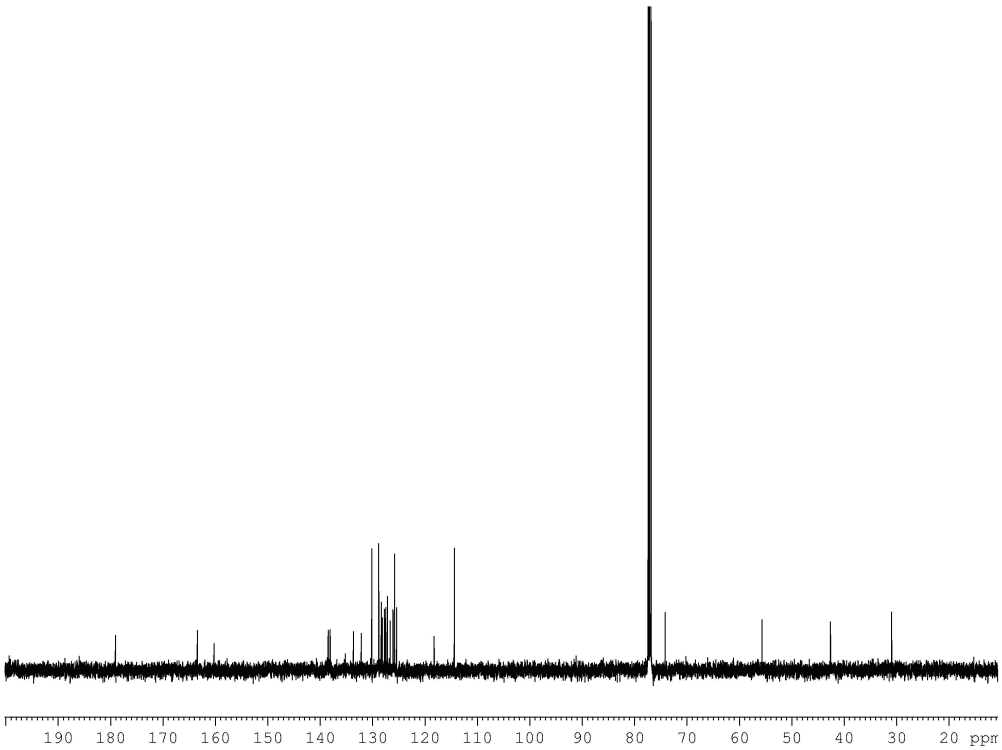
Scheme 3. ^{13}C NMR spectrum of compound **3** (125 MHz, $CDCl_3$)



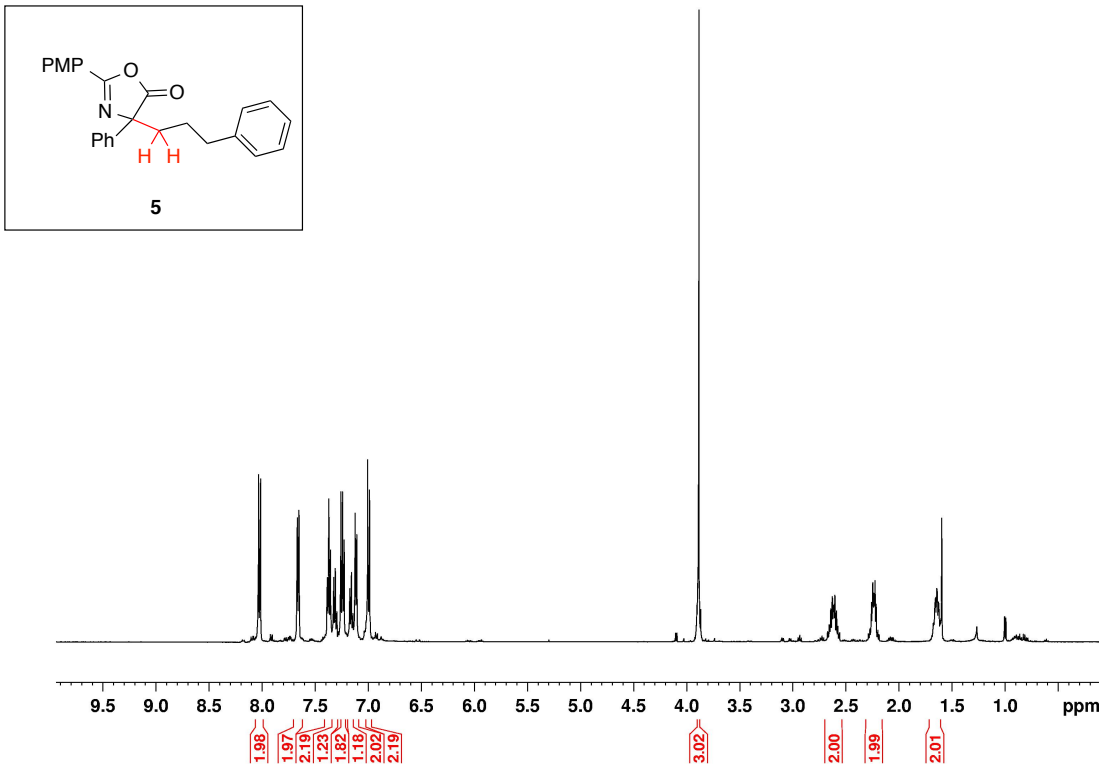
Scheme 4. ^{1}H NMR spectrum of compound **3** (500 MHz, $CDCl_3$)



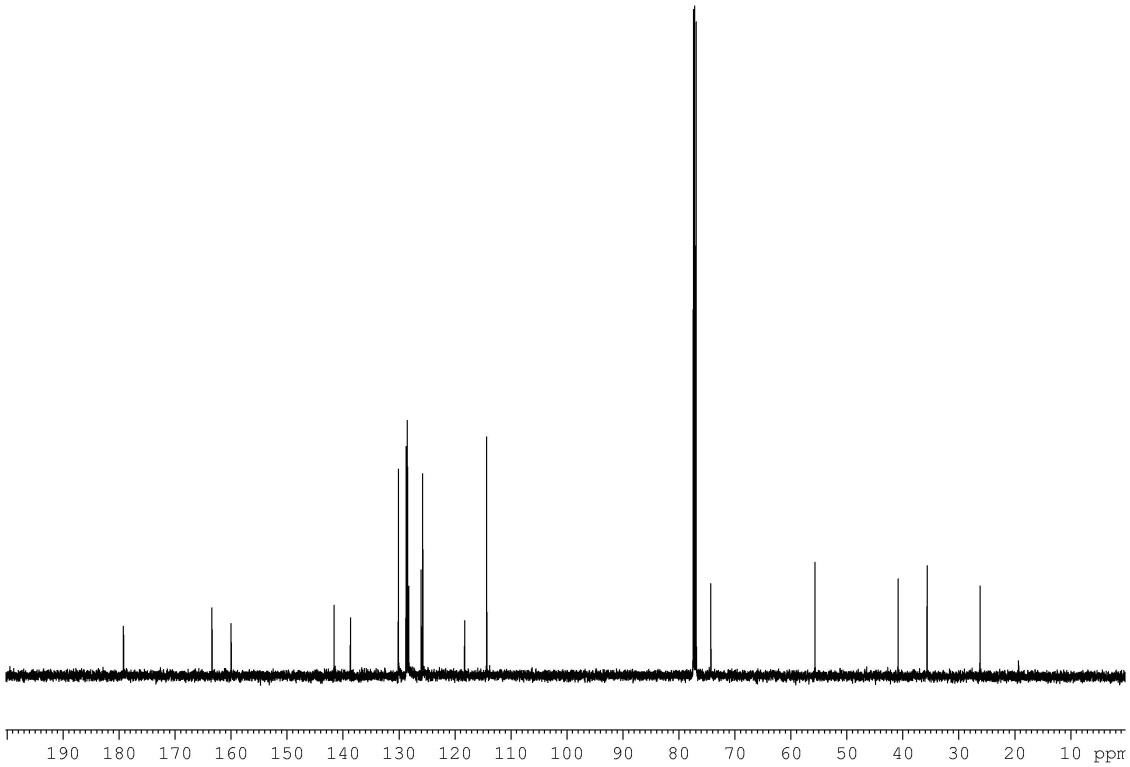
Scheme 3. ^{1}H NMR spectrum of compound **4** (500 MHz, $CDCl_3$)



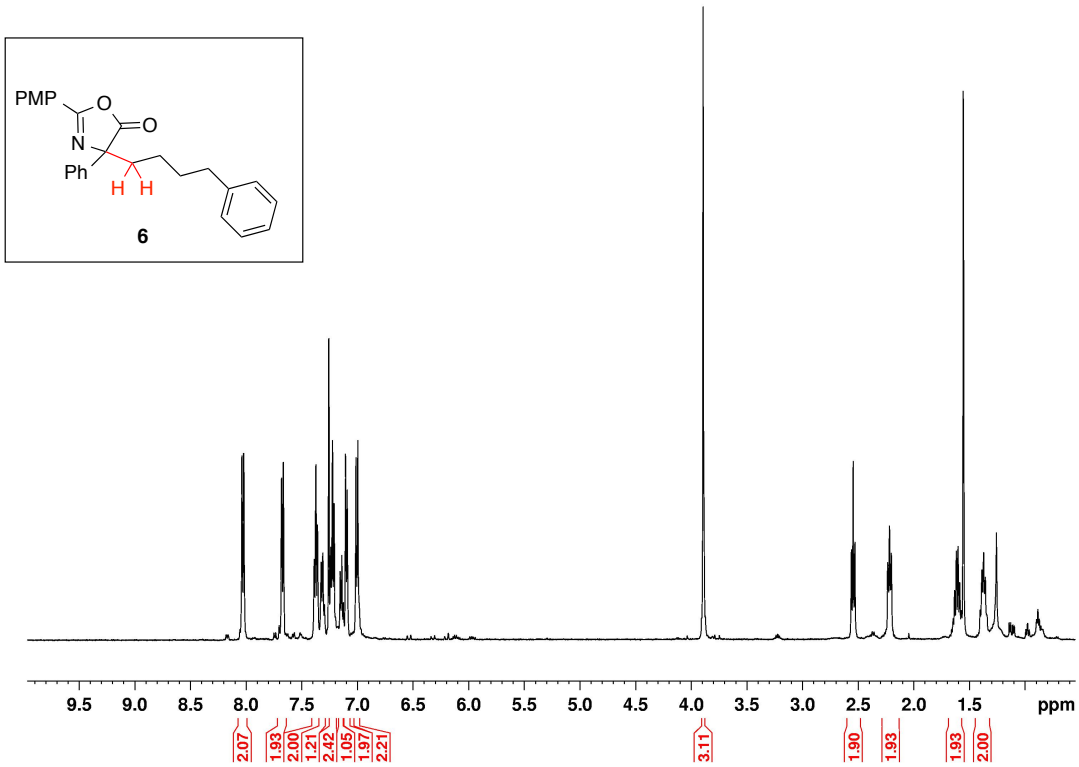
Scheme 3. ^{13}C NMR spectrum of compound **4** (125 MHz, $CDCl_3$)



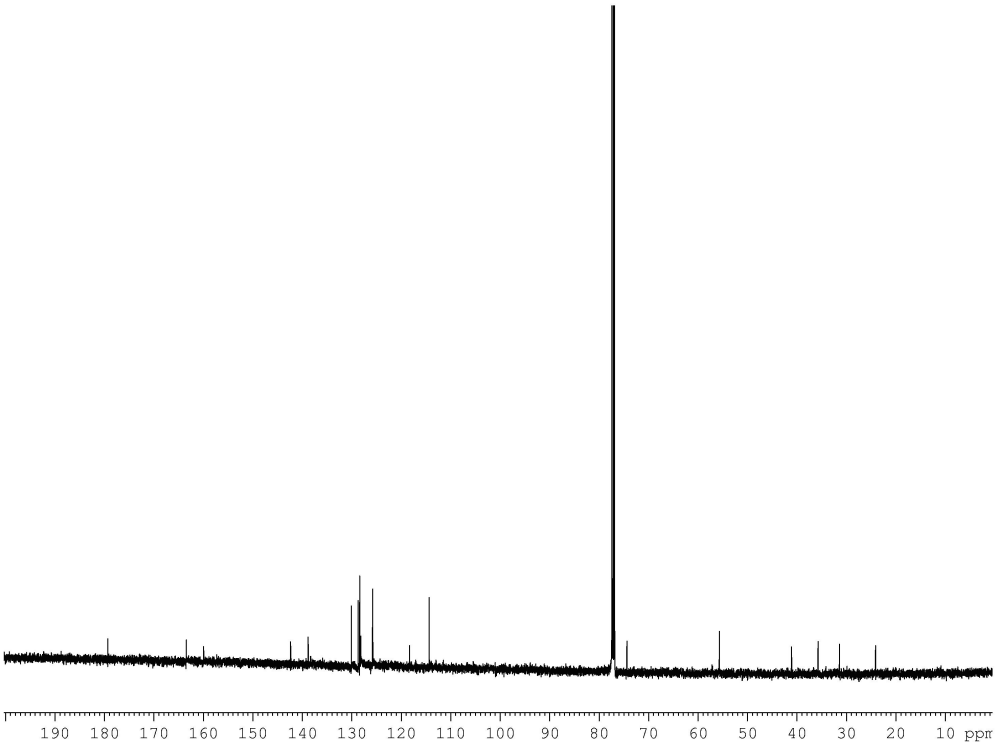
Scheme 3. ^{1}H NMR spectrum of compound **5** (500 MHz, $CDCl_3$)



Scheme 3. ^{13}C NMR spectrum of compound **5** (125 MHz, $CDCl_3$)



Scheme 3. ^{1}H NMR spectrum of compound **4** (500 MHz, $CDCl_3$)



Scheme 3. ^{13}C NMR spectrum of compound **6** (125 MHz, $CDCl_3$)